(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 February 2007 (15.02.2007)

PCT

(10) International Publication Number
WO 2007/017649 A1

(51) International Patent Classification:
C07D 403/12 (2006.01) *A61K 31/41* (2006.01)
C07D 405/14 (2006.01) *A61P 3/00* (2006.01)

(21) International Application Number: PCT/GB2006/002922

(22) International Filing Date: 7 August 2006 (07.08.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0516300.1	9 August 2005 (09.08.2005)	GB
0523860.5	24 November 2005 (24.11.2005)	GB

(71) Applicant (*for all designated States except MG, US*): **ASTRAZENECA AB** [SE/SE]; SE-151 85 Södertälje (SE).

(71) Applicant (*for MG only*): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **MCKERRECHER, Darren** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **PIKE, Kurt, Gordon** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **WARING, Michael, James** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, SE-151 85 Södertälje (SE).

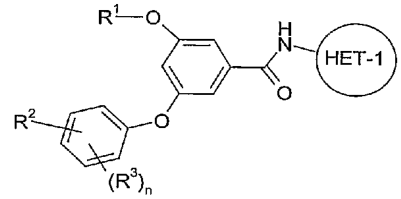
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROARYLCARBAMOYLBENZENE DERIVATIVES FOR THE TREATMENT OF DIABETES



(I)

(57) Abstract: Compounds of formula (I) wherein R_1, R_2, R_3 and HET-1 are as described in the specification, and their salts, are activators of glucokinase (GLK) and are thereby useful in the treatment of, for example, type 2 diabetes. Processes for preparing compounds of formula (I) are also described.

WO 2007/017649 A1

HETEROARYLCARBAMOYLBENZENE DERIVATIVES FOR THE TREATMENT OF DIABETES

The present invention relates to a group of benzoyl amino heterocyclyl compounds which are useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK or GK), leading to a decreased glucose threshold for insulin secretion. In addition the compounds are predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention also relates to pharmaceutical compositions comprising said compounds and to methods of treatment of diseases mediated by GLK using said compounds.

In the pancreatic β-cell and liver parenchymal cells the main plasma membrane glucose transporter is GLUT2. Under physiological glucose concentrations the rate at which GLUT2 transports glucose across the membrane is not rate limiting to the overall rate of glucose uptake in these cells. The rate of glucose uptake is limited by the rate of phosphorylation of glucose to glucose-6-phosphate (G-6-P) which is catalysed by glucokinase (GLK) [1]. GLK has a high (6-10mM) Km for glucose and is not inhibited by physiological concentrations of G-6-P [1]. GLK expression is limited to a few tissues and cell types, most notably pancreatic β-cells and liver cells (hepatocytes) [1]. In these cells GLK activity is rate limiting for glucose utilisation and therefore regulates the extent of glucose induced insulin secretion and hepatic glycogen synthesis. These processes are critical in the maintenance of whole body glucose homeostasis and both are dysfunctional in diabetes [2].

In one sub-type of diabetes, Maturity-Onset Diabetes of the Young Type 2 (MODY-2), the diabetes is caused by GLK loss of function mutations [3, 4]. Hyperglycaemia in MODY-2 patients results from defective glucose utilisation in both the pancreas and liver [5]. Defective glucose utilisation in the pancreas of MODY-2 patients results in a raised threshold for glucose stimulated insulin secretion. Conversely, rare activating mutations of GLK reduce this threshold resulting in familial hyperinsulinism [6, 6a, 7]. In addition to the reduced GLK activity observed in MODY-2 diabetics, hepatic glucokinase activity is also decreased in type 2 diabetics [8]. Importantly, global or liver selective overexpression of GLK prevents or reverses the development of the diabetic phenotype in both dietary and genetic models of the disease [9-12]. Moreover, acute

treatment of type 2 diabetics with fructose improves glucose tolerance through stimulation of hepatic glucose utilisation [13]. This effect is believed to be mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below [13].

Hepatic GLK activity is inhibited through association with GLK regulatory protein (GLKRP). The GLK/GLKRP complex is stabilised by fructose-6-phosphate (F6P) binding to the GLKRP and destabilised by displacement of this sugar phosphate by fructose-1-phosphate (F1P). F1P is generated by fructokinase mediated phosphorylation of dietary fructose. Consequently, GLK/GLKRP complex integrity and hepatic GLK activity is regulated in a nutritionally dependent manner as F6P is dominant in the post-absorptive state whereas F1P predominates in the post-prandial state. In contrast to the hepatocyte, the pancreatic β-cell expresses GLK in the absence of GLKRP. Therefore, β-cell GLK activity is regulated extensively by the availability of its substrate, glucose. Small molecules may activate GLK either directly or through destabilising the GLK/GLKRP complex. The former class of compounds are predicted to stimulate glucose utilisation in both the liver and the pancreas whereas the latter are predicted to act selectively in the liver. However, compounds with either profile are predicted to be of therapeutic benefit in treating Type 2 diabetes as this disease is characterised by defective glucose utilisation in both tissues.

GLK, GLKRP and the K_{ATP} channel are expressed in neurones of the hypothalamus, a region of the brain that is important in the regulation of energy balance and the control of food intake [14-18]. These neurones have been shown to express orectic and anorectic neuropeptides [15, 19, 20] and have been assumed to be the glucose-sensing neurones within the hypothalamus that are either inhibited or excited by changes in ambient glucose concentrations [17, 19, 21, 22]. The ability of these neurones to sense changes in glucose levels is defective in a variety of genetic and experimentally induced models of obesity [23-28]. Intracerebroventricular (icv) infusion of glucose analogues, that are competitive inhibitors of glucokinase, stimulate food intake in lean rats [29, 30]. In contrast, icv infusion of glucose suppresses feeding [31]. Thus, small molecule activators of GLK may decrease food intake and weight gain through central effects on GLK. Therefore, GLK activators may be of therapeutic use in treating eating disorders, including obesity, in addition to diabetes. The hypothalamic effects will be additive or

synergistic to the effects of the same compounds acting in the liver and/or pancreas in normalising glucose homeostasis, for the treatment of Type 2 diabetes. Thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity).

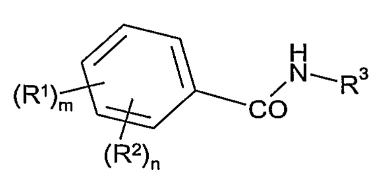
GLK is also expressed in specific entero-endocrine cells where it is believed to control the glucose sensitive secretion of the incretin peptides GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (Glucagon-Like Peptide-1) from gut K-cells and L-cells respectively (32, 33, 34). Therefore, small molecule activators of GLK may have additional beneficial effects on insulin secretion, b-cell function and survival and body weight as a consequence of stimulating GIP and GLP-1 secretion from these entero-endocrine cells.

In WO00/58293 and WO01/44216 (Roche), a series of benzylcarbamoyl compounds are described as glucokinase activators. The mechanism by which such compounds activate GLK is assessed by measuring the direct effect of such compounds in an assay in which GLK activity is linked to NADH production, which in turn is measured optically - see details of the *in vitro* assay described hereinafter. Compounds of the present invention may activate GLK directly or may activate GLK by inhibiting the interaction of GLKRP with GLK.

Further GLK activators have been described in WO03/095438 (substituted phenylacetamides, Roche), WO03/055482 (carboxamide and sulphonamide derivatives, Novo Nordisk), WO2004/002481 (arylcarbonyl derivatives, Novo Nordisk), and in WO03/080585 (amino-substituted benzoylaminoheterocycles, Banyu).

Our International application Number: WO03/000267 describes a group of benzoyl amino pyridyl carboxylic acids which are activators of the enzyme glucokinase (GLK).

Our International application Number: WO03/015774 describes compounds of the Formula (A):



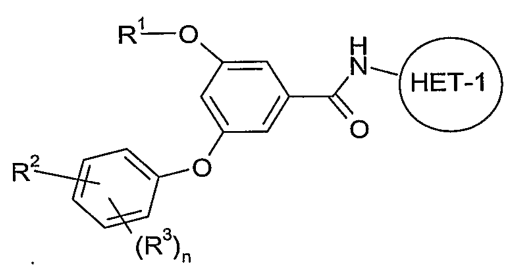
(A)

wherein R^3 is a substituted heterocycle other than a carboxylic acid substituted pyridyl.

International application WO2004/076420 (Banyu) describes compounds which are generally a subset of those described in WO03/015774, wherein for example R^1 is an (substituted) alkyl ether and R^2 is (substituted) phenoxy.

We have surprisingly found a small group of compounds, generally a selected subgroup of those described in WO 03/015774, which have generally superior potency for the GLK enzyme, and more advantageous physical properties, including, for example, higher aqueous solubility, higher permeability, and/or lower plasma protein binding. Consequently, such compounds having a balance of these properties would be expected to display higher plasma free drug levels and superior in vivo efficacy after oral dosing as determined, for example, by activity in Oral Glucose Tolerance Tests (OGTTs). Therefore this group of compounds would be expected to provide superior oral exposure at a lower dose and thereby be particularly suitable for use in the treatment or prevention of a disease or medical condition mediated through GLK. Furthermore, the compounds of the invention may have favourable metabolic profiles and/or toxicity profiles. The compounds of the invention may also have superior potency and/or advantageous physical properties (as described above) and/or favourable toxicity profiles and/or favourable metabolic profiles in comparison with other GLK activators known in the art, as well as those described in WO 03/015774.

Thus, according to the first aspect of the invention there is provided a compound of Formula (I):



(I)

wherein:

R^1 is selected from cyclopentyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl and 2-methoxybut-1-yl;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on any nitrogen atom (provided it is not thereby quaternised) by a substituent selected from R^7 and/or on 1 or 2 available carbon atoms by a substituent independently selected from R^6;

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

R^3 is halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 to 7 membered saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from R^8 and/or on an available nitrogen atom by a substituent selected from R^9; or

R^4 and R^5 together with the nitrogen atom to which they are attached form a 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon by 1 substituent selected from hydroxy, methyl and halo, or on an available nitrogen atom by methyl;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl;

R^7 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl;

R^8 is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl, aminocarbonyl, (1-4C)alkylaminocarbonyl, di(1-4C)alkylaminocarbonyl, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)p(1-4C)alkyl;

R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, aminocarbonyl, (1-4C)alkylaminocarbonyl, di(1-4C)alkylaminocarbonyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)p(1-4C)alkyl;

n is 0 or 1;

p is (independently at each occurrence) 0, 1 or 2;

or a salt thereof.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, wherein

R^1 is selected from but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl and 2-methoxybut-1-yl;

or a salt thereof.

It will be appreciated that, where the definition of heterocyclyl group HET-1 encompass heteroaryl rings which may be substituted on nitrogen, such substitution may not result in charged quaternary nitrogen atoms, removal of aromaticity of the ring or unstable structures. It will be appreciated that the definition of HET-1 is not intended to include any O-O, O-S or S-S bonds. It will be appreciated that the definition of HET-1 is not intended to include unstable structures.

It will be understood that any single carbon atom in HET-1 may only be substituted by one group R^6 in order to maintain aromaticity of the ring. Up to two different carbon atoms in a HET-1 ring may be substituted by an R^6 group, each of which may be the same or different, provided the structure thereby formed is stable and aromatic.

It will be understood that R^8 can be present on any or all available carbon atoms in the heterocyclic ring formed by NR^4R^5; each carbon atom can be substituted with 1 or 2 R^8 groups which may be the same or different, provided the structure thereby formed is stable (so, for example, it is not intended to cover gem-dihydroxy substitution).

It will be understood that where a compound of the formula (I) contains more than one group R^5, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^3, they may be the same or different.

A similar convention applies for all other groups and substituents on a compound of formula (I) as hereinbefore defined.

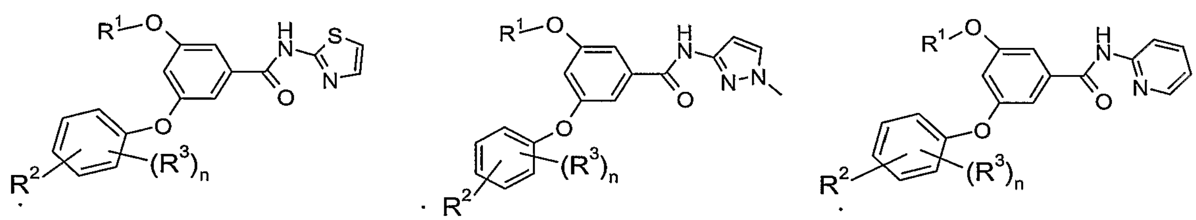
Compounds of Formula (I) may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pharmaceutically acceptable salt.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (I) are in-vivo hydrolysable esters of compounds of formula (I). Therefore in another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. An analogous convention applies to other generic terms.

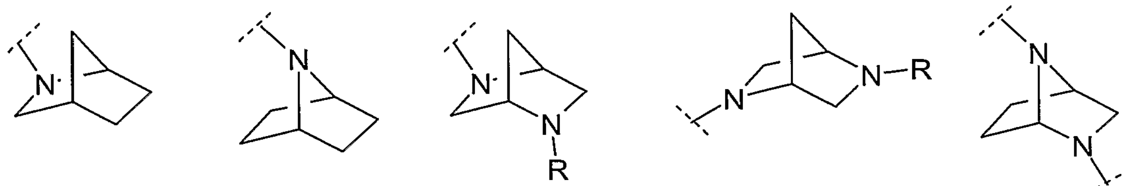
For the avoidance of doubt, reference to the group HET-1 containing a nitrogen in the 2-position, is intended to refer to the 2-position relative to the amide nitrogen atom to which the group is attached. For example, HET-1 encompasses but is not limited to the following structures:



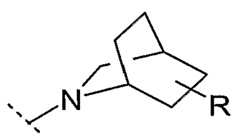
Suitable examples of HET-1 as a 5- or 6-membered, C-linked heteroaryl ring as hereinbefore defined, include thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl and triazolyl.

Suitable examples for a 4-7 membered ring formed by R^4 and R^5 together with the nitrogen to which they are attached, as hereinbefore defined, include morpholino, thiomorpholino (and versions thereof wherein the sulfur is oxidised to an SO or $S(O)_2$ group), piperidinyl, piperazinyl, pyrrolidinyl, azetidinyl, homopiperazinyl, homo-morpholino, homo-thiomorpholino (and versions thereof wherein the sulfur is oxidised to an SO or $S(O)_2$ group) and homo-piperidinyl.

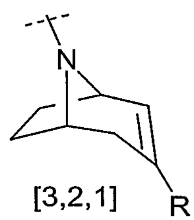
Suitable examples for a 6-10 membered bicyclic heterocyclic ring formed by R^4 and R^5 together with the nitrogen to which they are attached, as hereinbefore defined, are bicyclic saturated or partially unsaturated heterocyclyl ring such as those illustrated by the structures shown below (wherein the dotted line indicates the point of attachment to the rest of the molecule and wherein R represents the optional substituents on carbon or nitrogen defined hereinbefore):



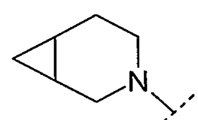
[2,2,1]



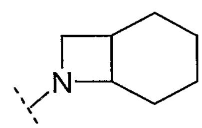
[2,2,2]



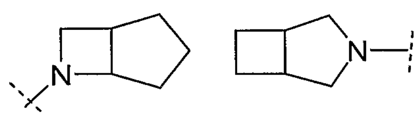
[3,2,1]



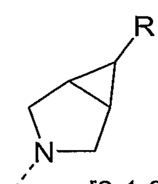
[4,1,0]



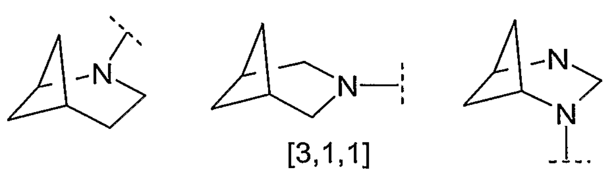
[4,2,0]



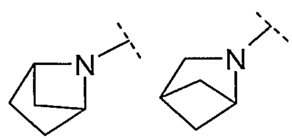
[3,2,0]



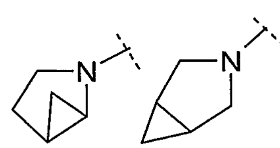
[3,1,0]



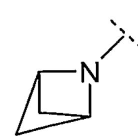
[3,1,1]



[2,1,1]

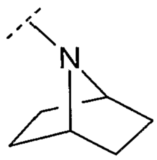


[3,1,0]



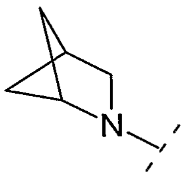
[1,1,1]

In particular such a ring system is a [2,2,1] system such as



(7-azabicyclo[2.2.1]hept-7-yl).

In another embodiment, such a ring system is a [2.1.1] system such as



(2-azabicyclo[2.1.1]hex-2-yl).

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl, isopropyl, butyl and tert-butyl; examples of **(3-6C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **halo** include fluoro, chloro, bromo and iodo; examples of **hydroxy(1-4C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl and 4-hydroxybutyl; examples of **(1-4C)alkoxy(1-4C)alkyl** include methoxymethyl, ethoxymethyl, tert-butoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, methoxypropyl, 2-methoxypropyl and methoxybutyl; example of **(1-4C)alkoxy** include methoxy, ehtoxy, propoxy, isopropxy, butoxy and tert-butoxy; examples of **(1-4C)alkylS(O)p(1-4C)alkyl (where p is 0, 1 or 2)** include methylsulfinylmethyl, ethylsulfinylmethyl, ethylsulfinylethyl, methylsulfinylpropyl, methylsulfinylbutyl, methylsulfonylmethyl, ethylsulfonylmethyl, ethylsulfonylethyl, methylsulfonylpropyl, methylsulfonylbutyl, methylthiomethyl, ethylthiomethyl, ethylthioethyl, methylthiopropyl, and methylthiobutyl; examples of **(1-4C)alkylsulfonyl** include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl and tert-butylsulfonyl; examples of **–S(O)p(1-4C)alkyl** include (1-4C)alkylsulfonyl, methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, tert-butylsulfinyl, methylthio, ethylthio, propylthio, isopropylthio and tert-butylthio; examples of **amino(1-4C)alkyl** include aminomethyl, aminoethyl, 2-aminopropyl, 3-aminopropyl, 1-aminoisopropyl and 4-aminobutyl; examples of **(1-4C)alkylamino(1-4C)alkyl** include (N-methyl)aminomethyl, (N-ethyl)aminomethyl, 1-((N-methyl)amino)ethyl, 2-((N-methyl)amino)ethyl, (N-ethyl)aminoethyl, (N-methyl)aminopropyl, and 4-((N-methyl)amino)butyl; examples of **di(1-4C)alkylamino(1-4C)alkyl** include

dimethylaminomethyl, methyl(ethyl)aminomethyl, methyl(ethyl)aminoethyl, (N,N-diethyl)aminoethyl, (N,N-dimethyl)aminopropyl and (N,N-dimethyl)aminobutyl; examples of **–C(O)(1-4C)alkyl** and **(1-4C)alkylcarbonyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl and tert-butyl carbonyl; examples of **(1-4C)alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, butylamino and tert-butylamino; examples of **di(1-4C)alkylamino** include dimethylamino, diethylamino, N-methyl-N-ethylamino, dipropylamino, N-isopropyl-N-methyamino and dibutylamino; examples of **(1-4C)alkylaminocarbonyl** include methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl, butylaminocarbonyl and tert-butylaminocarbonyl; examples of **di(1-4C)alkylaminocarbonyl** include dimethylaminocarbonyl, diethylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, dipropylaminocarbonyl, N-isopropyl-N-methyaminocarbonyl and dibutylaminocarbonyl.

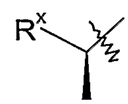
It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of stimulating GLK directly or inhibiting the GLK/GLKRP interaction. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. It is also to be understood that certain compounds may exist in tautomeric forms and that the invention also relates to any and all tautomeric forms of the compounds of the invention which activate GLK.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which activate GLK.

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

Preferred values of each variable group are as follows. Such values may be used where appropriate with any of the values, definitions, claims, aspects or embodiments defined hereinbefore or hereinafter. In particular, each may be used as an individual limitation on the broadest definition of formula (I). Further, each of the following values may be used in combination with one or more of the other following values to limit the broadest defintion of formula (I).

(1) R^1 is of sub-formula X:



(X)

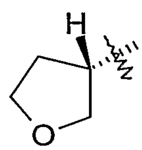
wherein R^x is selected from ethyl, trifluoromethyl, ethynyl and hydroxyethyl

(2) R^1 is selected from 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl and 2-hydroxybut-1-yl

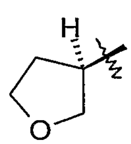
(3) R^1 is 1,1,1-trifluoroprop-2-yl

(4) R^1 is tetrahydrofuryl or tetrahydropyranyl

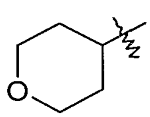
(5) R^1 is tetrahydrofuryl in the (S) configuration, that is:



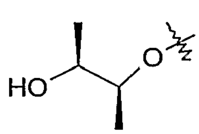
(6) R^1 is tetrahydrofuryl in the (R) configuration, that is:



(7) R^1 is 4-tetrahydropyranyl:



(8) R^1 is 2-hydroxy-but-3-yl and the configuration is preferably such that R^1-O- is:



(9) R^1 is selected from 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl and but-2-yl

(10) R^1 is selected from 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl and 2-methoxybut-1-yl;

(11) R^1 is selected from 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, cyclopentyl and but-2-yl

(12) R^1 is 2-hydroxybut-1-yl

(13) R^1 is 1,3-difluoroprop-2-yl

(14) HET-1 is a 5-membered heteroaryl ring

(15) HET-1 is a 6-membered heteroaryl ring

(16) HET-1 is substituted with 1 or 2 substituents independently selected from R^6

(17) HET-1 is substituted with 1 substituent selected from R^6

(18) HET-1 is substituted with 1 substituent selected from R^7

(19) HET-1 is unsubstituted

(20) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, and triazolyl

(21) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl

(22) HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl

(23) HET-1 is selected from thiazolyl, pyrazolyl and oxazolyl

(24) HET-1 is selected from thiadiazolyl and oxadiazolyl

(25) HET-1 is selected from 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl

(26) HET-1 is selected from 1,2,4-oxadiazolyl and 1,2,4-oxadiazolyl

(27) HET-1 is pyrazolyl, particularly N-methylpyrazolyl

(28) HET-1 is pyrazolyl, optionally substituted with a methyl group on an available carbon or nitrogen atom, particularly on a carbon atom

(29) HET-1 is pyrazinyl

(30) HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl;

(31) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl

(32) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl

(33) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, and di(1-4C)alkylamino(1-4C)alkyl

(34) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl and methoxymethyl

(35) R^6 is selected from methyl, ethyl, chloro and fluoro

(36) R^6 is methyl

(37) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, dimethylaminomethyl, hydroxymethyl and methoxymethyl

(38) R^6 is selected from methyl, ethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl, hydroxymethyl and methoxymethyl

(39) R^6 is selected from methyl, ethyl, isopropyl and methoxymethyl

(40) when 2 substituents R^6 are present, both are selected from methyl, ethyl, bromo, chloro and fluoro; preferably both are methyl

(41) R^6 is selected from (1-4C)alkylS(O)p(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl

(42) R^7 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl

(43) R^7 is selected from methyl, ethyl, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl

(44) R^7 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, and di(1-4C)alkylamino(1-4C)alkyl

(45) R^7 is selected from methyl, ethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl

(46) R^7 is selected from methyl, ethyl, hydroxymethyl and methoxymethyl

(47) R^7 is selected from methyl and ethyl

(48) R^7 is methyl

(49) R^7 is selected from methyl, ethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl, hydroxymethyl and methoxymethyl

(50) R^7 is selected from methyl, ethyl, isopropyl and methoxymethyl

(51) R^3 is chloro or fluoro

(52) R^3 is chloro

(53) R^3 is fluoro

(54) R^2 is –C(O)NR^4R^5

(55) R^2 is -$SO_2NR^4R^5$

(56) R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 membered ring

(57) R^4 and R^5 together with the nitrogen atom to which they are attached form a 5 membered ring

(58) R^4 and R^5 together with the nitrogen atom to which they are attached form a 6 membered ring

(59) R^4 and R^5 together with the nitrogen atom to which they are attached form a 7 membered ring

(60) R^4 and R^5 together with the nitrogen atom to which they are attached form a fully saturated ring

(61) R^4 and R^5 together with the nitrogen atom to which they are attached form a ring selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(62) R^4 and R^5 together with the nitrogen atom to which they are attached form a ring selected from pyrrolidinyl, morpholino and azetidinyl

(63) R^4 and R^5 together with the nitrogen atom to which they are attached form an azetidinyl ring

(64) R^4 and R^5 together with the nitrogen atom to which they are attached form an unsubstituted ring

(65) R^4 and R^5 together with the nitrogen atom to which they are attached form an ring mono-substituted either with a substituent R^8 or with a substituent R^9

(66) R^4 and R^5 together with the nitrogen atom to which they are attached form a 6-10 membered bicyclic saturated or partially unsaturated ring

(67) R^8 is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl

(68) R^8 is selected from hydroxy, methoxy and methyl

(69) R^9 is selected from (1-4C)alkyl and –C(O)(1-4C)alkyl

(70) R^2 is azetidinylcarbonyl

(71) n = 0

(72) n = 1

According to a further feature of the invention there is provided the following preferred groups of compounds of the invention:

In one aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl and 2-methoxybut-1-yl;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on any nitrogen atom (provided it is not thereby quaternised) by a substituent selected from R^7 and/or on 1 or 2 available carbon atoms by a substituent independently selected from R^6;

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

R^3 is halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 to 7 membered saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from R^8 and/or on an available nitrogen atom by a substituent selected from R^9;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl;

R^7 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl;

R^8 is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl, aminocarbonyl, (1-4C)alkylaminocarbonyl, di(1-4C)alkylaminocarbonyl, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)p(1-4C)alkyl;
R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, aminocarbonyl, (1-4C)alkylaminocarbonyl, di(1-4C)alkylaminocarbonyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)p(1-4C)alkyl;
n is 0 or 1;
p is (independently at each occurrence) 0, 1 or 2;
or a salt thereof.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:
R^1 is selected from cyclopentyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;
HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;
R^2 is $-CONR^4R^5$;
n is 0;
R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:
R^1 is selected from but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;
HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;
R^2 is $-CONR^4R^5$;
n is 0;
R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from cyclopentyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;
HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein HET-1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;
n is 0 or 1;
R^3 is fluoro or chloro;
R^2 is $-CONR^4R^5$;
R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:
R^1 is selected from but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;
HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein HET-1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;
n is 0 or 1;
R^3 is fluoro or chloro;
R^2 is $-CONR^4R^5$;
R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In one aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:
R^1 is selected from cyclopentyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;
HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;
R^2 is $-SO_2NR^4R^5$;
n is 0;
R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In one aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;
HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;
R^2 is $-SO_2NR^4R^5$;
n is 0;
R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:
R^1 is selected from cyclopentyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;
HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein HET-1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;
n is 0 or 1;
R^3 is fluoro or chloro;
R^2 is $-SO_2NR^4R^5$;
R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:
R^1 is selected from but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;
HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein HET-1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;
n is 0 or 1;
R^3 is fluoro or chloro;
R^2 is $-SO_2NR^4R^5$;
R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:
R^1 is selected from 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl and but-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein HET-1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;

n is 0 or 1;

R^3 is fluoro or chloro;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl and but-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein HET-1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;

n is 0 or 1;

R^3 is fluoro or chloro;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from cyclopentyl, 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl and but-2-yl;

HET-1 is N-methylpyrazolyl;

n is 0 or 1;

R^3 is chloro;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl and but-2-yl;

HET-1 is N-methylpyrazolyl;

n is 0 or 1;

R^3 is chloro;

R^2 is –CONR^{4}R^5;

R^4 and R^5 together form an azetidinyl ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from cyclopentyl, 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl and but-2-yl;

HET-1 is pyrazolyl, optionally substituted on carbon or nitrogen by a methyl group;

n is 0 or 1;

R^3 is fluoro or chloro;

R^2 is –CONR^{4}R^5;

R^4 and R^5 together form an azetidinyl ring.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from cyclopentyl, 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl and but-2-yl;

HET-1 is pyrazolyl or 5-methylpyrazol-3-yl;

n is 0 or 1;

R^3 is fluoro or chloro, particularly chloro;

R^2 is –CONR^{4}R^5;

R^4 and R^5 together form an azetidinyl ring.

Further preferred compounds of the invention are each of the Examples, each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples.

Particular compounds of the invention include any one or more of:

3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(2R)-2-hydroxybutyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide;

3-{[4-(azetidin-1-ylcarbonyl)-2-fluorophenyl]oxy}-5-{[(1R,2R)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[4-(azetidin-1-ylcarbonyl)-2-fluorophenyl]oxy}-5-{[(1S,2S)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1R,2R)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1S,2S)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1R,2R)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1S,2S)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1S)-1-methylprop-2-yn-1-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1S)-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and/or
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-(cyclopentyloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-(cyclopentyloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and/or
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-N-(5-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-N-1H-pyrazol-3-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
or a pharmaceutically-acceptable salt thereof.

The compounds of the invention may be administered in the form of a pro-drug. A pro-drug is a bioprecursor or pharmaceutically acceptable compound being degradable in the body to produce a compound of the invention (such as an ester or amide of a compound of the invention, particularly an in-vivo hydrolysable ester).

Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen;

c) H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

The contents of the above cited documents are incorporated herein by reference.

Examples of pro-drugs are as follows. An in-vivo hydrolysable ester of a compound of the invention containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_1 to C_6alkoxymethyl esters for example methoxymethyl, C_1 to C_6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_3 to C_8cycloalkoxycarbonyloxyC_1 to C_6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic,

for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a benzoxazinone derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A further feature of the invention is a pharmaceutical composition comprising a compound of Formula (I) as defined above, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically-acceptable diluent or carrier.

According to another aspect of the invention there is provided a compound of Formula (I) as defined above or a pharmaceutically-acceptable salt thereof for use as a medicament.

According to another aspect of the invention there is provided a compound of Formula (I), or a pharmaceutically-acceptable salt thereof as defined above for use as a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

Further according to the invention there is provided the use of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof in the preparation of a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

The compound is suitably formulated as a pharmaceutical composition for use in this way.

According to another aspect of the present invention there is provided a method of treating GLK mediated diseases, especially diabetes, by administering an effective amount of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

Specific diseases which may be treated by a compound or composition of the invention include: blood glucose lowering in Type 2 Diabetes Mellitus without a serious risk of hypoglycaemia (and potential to treat type 1), dyslipidemia, obesity, insulin resistance, metabolic syndrome X, impaired glucose tolerance.

As discussed above, thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity). Thus, according to another aspect of the invention there is provided the use of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in the combined treatment or prevention, particularly treatment, of diabetes and obesity.

According to another aspect of the invention there is provided the use of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in the treatment or prevention of obesity.

According to a further aspect of the invention there is provided a method for the combined treatment of obesity and diabetes by administering an effective amount of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

According to another aspect of the invention there is provided a compound of Formula (I) or a pharmaceutically-acceptable salt thereof as defined above for use as a medicament for treatment or prevention, particularly treatment of obesity.

According to a further aspect of the invention there is provided a method for the treatment of obesity by administering an effective amount of a compound of Formula (I) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

Compounds of the invention may be particularly suitable for use as pharmaceuticals because of advantageous physical and/or pharmacokinetic properties, and/or favourable toxicity profile.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing). Dosage forms suitable for oral use are preferred.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions

intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol

containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The elevation of GLK activity described herein may be applied as a sole therapy or in combination with one or more other substances and/or treatments for the indication being treated. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus, chemotherapy may include the following main categories of treatment:

1) Insulin and insulin analogues;

2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide);

3) Agents that improve incretin action (for example dipeptidyl peptidase IV inhibitors, and GLP-1 agonists);

4) Insulin sensitising agents including PPARgamma agonists (for example pioglitazone and rosiglitazone), and agents with combined PPARalpha and gamma activity;

5) Agents that modulate hepatic glucose balance (for example metformin, fructose 1, 6 bisphosphatase inhibitors, glycogen phopsphorylase inhibitors, glycogen synthase kinase inhibitors);

6) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

7) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors);

8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors);

9) Anti-obesity agents (for example sibutramine and orlistat);

10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (eg statins); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);

11) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;

13) Agents which antagonise the actions of glucagon; and

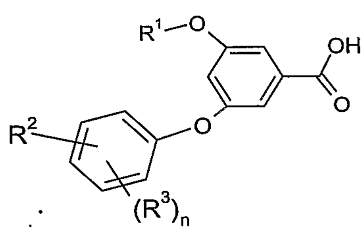
14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

According to another aspect of the present invention there is provided individual compounds produced as end products in the Examples set out below and salts thereof.

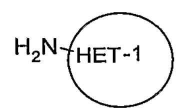
A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991.

Processes for the synthesis of compounds of Formula (I) are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I), which comprises a process a) to e) (wherein the variables are as defined hereinbefore for compounds of Formula (I) unless otherwise defined):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV), wherein R^1 is as hereinbefore defined or a protected version thereof;



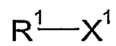
(III)

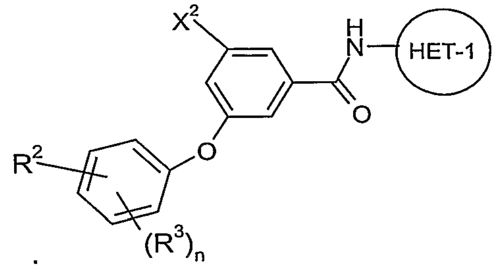


(IV);

or

(b) reaction of a compound of Formula (V) with a compound of Formula (VI),

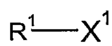


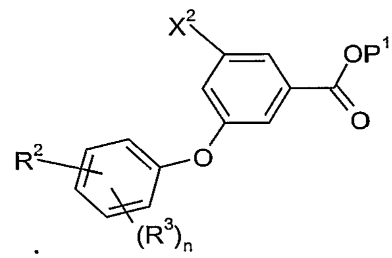


(V) (VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group, and wherein R^1 is as hereinbefore defined or a protected version thereof;

process (b) could also be accomplished using the intermediate ester Formula (VII), wherein P^1 is a protecting group as hereinafter described, followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;

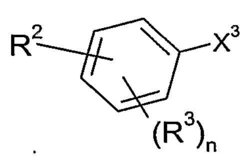


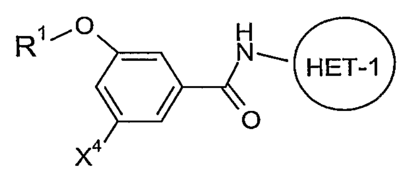


(V) (VII)

or

(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)

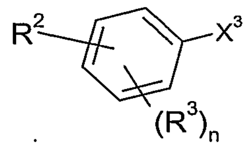


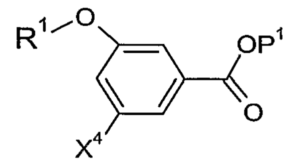


(VIII) (IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent, and wherein R^1 is as hereinbefore defined or a protected version thereof;

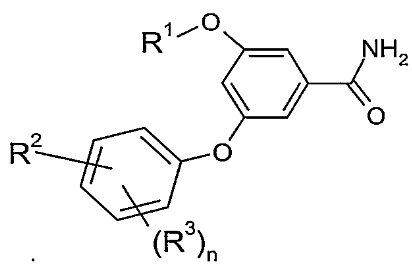
process (c) could also be accomplished using the intermediate ester Formula (X), followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;

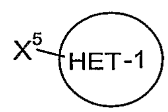




(VIII) (X)

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),

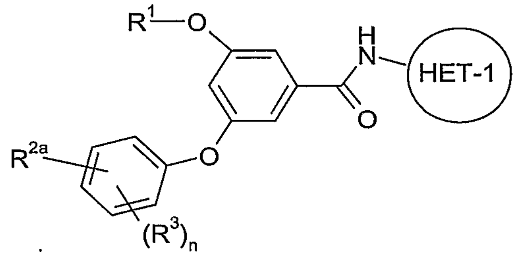




(XI) (XII);

wherein X^5 is a leaving group; and wherein R^1 is as hereinbefore defined or a protected version thereof; or

e) reaction of a compound of formula (XIII)



(XIII)

wherein R^{2a} is a precursor to R^2, such as a carboxylic acid, ester or anhydride (for R^2 = $-CONR^4R^5$) or the sulfonic acid equivalents (for R^2 is $-SO^2NR^4R^5$); with an amine of formula $-NR^4R^5$;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt thereof.

Suitable leaving groups X^1 to X^5 for processes b) to d) are any leaving group known in the art for these types of reactions, for example halo, alkoxy, trifluoromethanesulfonyloxy, methanesulfonyloxy, or p-toluenesulfonyloxy; or a group (such as a hydroxy group) that may be converted into a leaving group (such as an oxytriphenylphosphonium group) *in situ*.

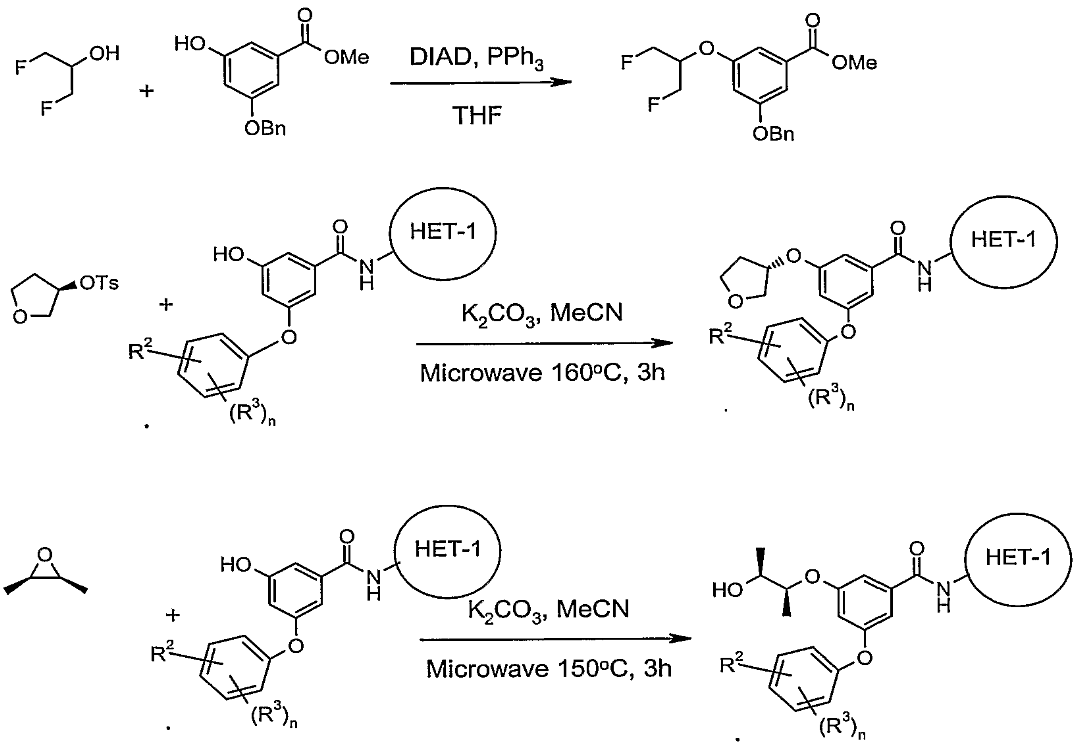
Suitable values for R^1 containing a protected hydroxy group are any suitable protected hydroxy group known in the art, for example simple ethers such as a methyl ether, tert-butyl ether or silylethers such as –OSi[(1-4C)alkyl]$_3$ (wherein each (1-4C)alkyl group is independently selected from methyl, ethyl, propyl, isopropyl, and tertbutyl). Examples of such trialkylsilyl groups are trimethylsilyl, triethylsilyl, triisopropylsilyl and tert-butyldimethylsilyl. Further suitable silyl ethers are those containing phenyl and substituted phenyl groups, such as –Si(PhMe$_2$) and –Si(TolMe$_2$) (wherein Tol = methylbenzene). Further suitable values for hydroxy protecting groups are given hereinafter.

Compounds of Formulae (III) to (XII) are commercially available, or are known in the art, or may be made by processes known in the art, for example as shown in the accompanying Examples, or as described below. For further information on processes for making such compounds, we refer to our PCT publications WO 03/000267, WO 03/015774 and WO 03/000262 and references therein. In general it will be appreciated that any aryl-O or alkyl-O bond may be formed by nucleophilic substitution or metal catalysed processes, optionally in the presence of a suitable base.

Compounds of Formula (XIII) may be made by processes such as those shown in processes a) to d) and/or by those processes mentioned above for compounds of formulae (III) to (XII).

The group R^1 in the compounds of formulae (III), (IX), (X), (XI) and (XIII) may be made by reaction of suitable precursors with compounds of formula (V) or derivatives thereof, depending on the nature of the R^1 group, for example, by nucleophilic displacement of a leaving group X^1 in a compound of formula (V). Compounds of formula (V) are generally commercially available or maybe made by simple functional group interconversions from comercially available compounds, or by literature methods. Further information is available in WO2004/076420, WO2005/054200, WO2005/054233, WO 2005/044801 and WO 2005/056530. Some illustrative examples using various R^1 groups are given in the Schemes

below, and/or in the accompanying examples, and may generally be applied analogously to R^1 groups not shown below.



[PG is protecting group, Ts is p-toluenesulfonyl].

Examples of conversions of a compound of Formula (I) into another compound of Formula (I), well known to those skilled in the art, include functional group interconversions such as hydrolysis, hydrogenation, hydrogenolysis, oxidation or reduction, and/or further functionalisation by standard reactions such as amide or metal-catalysed coupling, or nucleophilic displacement reactions.

It will be understood that substituents R^3, R^6 and/or R^7 may be introduced into the molecule at any convenient point in the synthetic sequence or may be present in the starting materials. A precursor to one of these substituents may be present in the molecule during the process steps a) to e) above, and then be transformed into the desired substituent as a final step to form the compound of formula (I); followed where necessary by

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt thereof.

Specific reaction conditions for the above reactions are as follows, wherein when P^1 is a protecting group P^1 is preferably (1-4C)alkyl, for example methyl or ethyl:

Process a) – coupling reactions of amino groups with carboxylic acids to form an amide are well known in the art. For example,

(i) using an appropriate coupling reaction, such as a carbodiimide coupling reaction performed with EDAC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) in the presence of dimethylaminopyridine (DMAP) in a suitable solvent such as dichloromethane (DCM), chloroform or dimethylformamide (DMF) at room temperature; or

(ii) reaction in which the carboxylic group is activated to an acid chloride by reaction with oxalyl chloride in the presence of a suitable solvent such as DCM. The acid chloride can then be reacted with a compound of Formula (IV) in the presence of a base, such as triethylamine or pyridine, in a suitable solvent such as chloroform or DCM at a temperature between 0°C and 80°C.

Process b) – compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as DMF or tetrahydrofuran (THF), with a base such as sodium hydride or potassium *tert*-butoxide, at a temperature in the range 0 to 200°C, optionally using microwave heating or metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; alternatively, compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as THF or DCM, with a suitable phosphine such as triphenylphosphine, and azodicarboxylate such as diethylazodicarboxylate; process b) could also be carried out using a precursor to the ester of formula (VII) such as an aryl-nitrile or trifluoromethyl derivative, followed by conversion to a carboxylic acid and amide formation as previously described;

Process c) - compounds of Formula (VIII) and (IX) can be reacted together in a suitable solvent, such as DMF or THF, with a base such as sodium hydride or potassium tert-butoxide, at a temperature in the range 0 to 200°C, optionally using microwave heating or metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; process c) could also be carried out using a precursor to the ester of formula (X) such as an aryl-nitrile or trifluoromethyl derivative, followed by conversion to a carboxylic acid and amide formation as previously described;

compounds of the formula (VIII) are commercially available or can be prepared from commercially available materials by processes well known to those skilled in the art, for example functional group interconversions (such as hydrolysis, hydrogenation, hydrogenolysis, oxidation or reduction), and/or further functionalisation and/or cyclisation by standard reactions (such as amide or sulphonamide or metal-catalysed coupling, or nucleophilic displacement or electrophilic substitution reactions);

Process d) – reaction of a compound of Formula (XI) with a compound of Formula (XII) can be performed in a polar solvent, such as DMF or a non-polar solvent such as THF with a strong base, such as sodium hydride or potassium *tert*-butoxide at a temperature between 0 and 200°C, optionally using microwave heating or metal catalysis, such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide;

Process e) - coupling reactions of amino groups with carboxylic or sulfonic acids or acid derivatives to form an amide are well known in the art and are described above for Process a).

Certain intermediates of formula (III), (VI), (VII), (IX) and/or (XI) are believed to be novel and comprise an independent aspect of the invention.

Certain intermediates of formula (III), (IX) and/or (XI) wherein R^1 is as defined herein for a compound of formula (I) are believed to be novel and comprise an independent aspect of the invention.

Certain intermediates of formula (XIII) are believed to be novel and comprise an independent aspect of the invention.

During the preparation process, it may be advantageous to use a protecting group for a functional group within the molecule. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are

similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (e.g. isopropyl, t-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis. Hydrogenation may also be used.

Examples of hydroxy protecting groups include methyl, t-butyl, lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl); tetrahydropyran-2-yl; aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (e.g. trimethylsilyl and t-butyldimethylsilyl); alkylidene (e.g. methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, hydrogenation, nucleophilic displacement, acid-, base, metal- or enzymically-catalysed hydrolysis, catalytic hydrogenolysis or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups. For example, methylether protecting groups for hydroxy groups may be removed by trimethylsilyliodide. A tert-butyl ether protecting group for a hydroxy group may be removed by hydrolysis, for example by use of hydrochloric acid in methanol.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyldimethylsily, t-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyldimethylsilyloxymethyl, t-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred aspects and embodiments of the compounds of the invention described herein also apply.

The following examples are for illustration purposes and are not intended to limit the scope of this application. Each exemplified compound represents a particular and independent aspect of the invention. In the following non-limiting Examples, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in *vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) with a field strength (for proton) of 300MHz (generally using a Varian Gemini 2000) or 400 MHz (generally using a Bruker Avance DPX400), unless otherwise stated, and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) Purification by chromatography generally refers to flash column chromatography, on silica unless otherwise stated. Column chromatography was generally carried out using prepacked silica cartridges (from 4g up to 400g) such as Redisep™ (available, for example, from Presearch Ltd, Hitchin, Herts, UK) or Biotage (Biotage UK Ltd, Hertford, Herts, UK), eluted using a pump and fraction collector system. Purification by Solid Phase Extraction (SPE) methods generally refers to the use of chromatography cartridges packed with SPE materials such as ISOLUTE® SCX-2 columns (available, for example, From International Sorbent Technology Ltd, Dryffryn Business Park, Hengoed, Mid Glamorgan, UK);

(vii) Mass spectra (MS) data was generated on an LCMS system where the HPLC component comprised generally either a Agilent 1100 or Waters Alliance HT (2790 & 2795) equipment and was run on a Phemonenex Gemini C18 5μm, 50 x 2 mm column (or similar) eluting with either acidic eluent (for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 1% formic acid in 50:50 water:acetonitrile (v/v) mixture; or using an equivalent solvent system with methanol instead of acetonitrile), or basic eluent

(for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 0.1% 880 Ammonia in acetonitrile mixture); and the MS component comprised generally a Waters ZQ spectrometer. Chromatograms for Electrospray (ESI) positive and negative Base Peak Intensity, and UV Total Absorption Chromatogram from 220-300nm, are generated and values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is $(M-H)^-$;

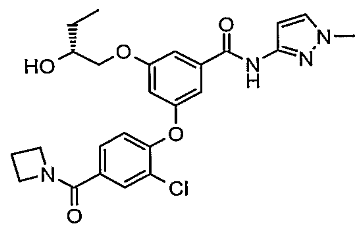
(viii) Suitable microwave reactors include "Smith Creator", "CEM Explorer", "Biotage Initiator sixty" and "Biotage Initiator eight".

Abbreviations

DCM	dichloromethane
DEAD	diethylazodicarboxylate
DIAD	diisopropylazodicarboxylate
DIPEA	*N,N*-diisopropylethylamine
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
EDAC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexofluorophosphate
HPLC	high pressure liquid chromatography
HPMC	hydroxypropylmethylcellulose
LCMS	liquid chromatography / mass spectroscopy
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
RT	room temperature
THF	tetrahydrofuran
TFA	trifluoroacetic acid
$CDCl_3$	deuterochloroform

All compound names were derived using ACD NAME computer package.

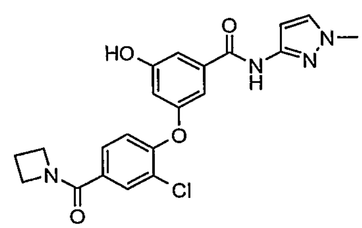
Example 1: 3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(2*R*)-2-hydroxybutyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A mixture of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.1 g, 0.23 mmol), (R)-(+)-1,2-epoxybutane (0.08 mL, 0.93 mmol) and potassium carbonate (81 mg, 0.59 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave' for 4 hours. The mixture was allowed to reach RT and pressure and reduced *in vacuo*. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The ethyl acetate layer was separated, washed with water (50 mL) brine (50 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate, to give the desired compound (47 mg).
^{1}H NMR δ ($CDCl_3$): 1.03 (t, 3H), 1.61 (quin, 2H), 2.38 (quin, 2H), 3.79 (s, 3H), 3.89 (m, 2H), 4.01 (m, 1H), 4.20-4.40 (m, 4H), 6.70 (m, 1H), 6.79 (m, 1H), 7.04 (m, 2H), 7.20 (m, 1H), 7.30 (m, 1H), 7.51 (dd, 1H), 7.79 (m, 1H), 8.48 (s, 1H); *m/z* 499 $(M+H)^+$

The preparation of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described below:

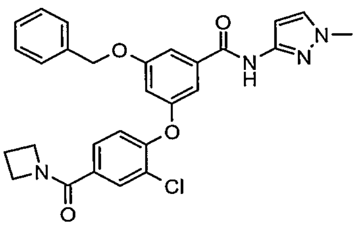
3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



Triethylamine (0.24 mL, 1.04 mmol) and triethylsilane (6.03 mL, 34.8 mmol) were added to palladium (II) acetate (72 mg, 18 mol%) in DCM (18 mL) under an atmosphere of argon. The reaction was stirred for 15 mins then 3-{[4-(azetidin-1-ylcarbonyl)-2-

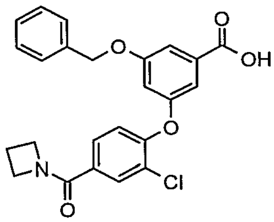
chlorophenyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (0.9 g, 1.74 mmol) in DCM (18 mL) was added dropwise and stirred for a further 2 hours. Methanol (20 mL) was added and the reaction filtered through Celite® and the filtrate concentrated *in vacuo*. Ethyl acetate (50 mL) was added and the organincs washed with water (40 mL), 1M hydrochloric acid (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a residue which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (0.4 g). ^{1}H NMR δ ($CDCl_3$): 2.38 (m, 2H), 3.83 (s, 3H), 4.20-4.40 (m, 4H), 6.63 (m, 1H), 6.76 (m, 1H), 7.02 (m, 2H), 7.20 (m, 1H), 7.28 (m, 1H), 7.50 (d, 1H), 7.77 (m, 1H), 8.02 (s, 1H), 8.55 (s, 1H); *m/z* 427 $(M+H)^+$

3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



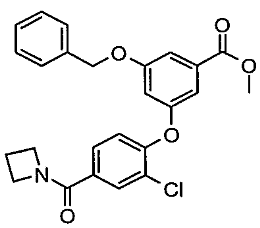
DIPEA (2.1 mL, 11.24 mmol) was added to a suspension of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (1.23 g, 2.81 mmol), HATU (2.23 g, 5.90 mmol) and 3-amino-1-methylpyrazole (0.54mg, 5.62 mmol) in DMF (15 mL). The resulting mixture was stirred at RT for 24 hours. The DMF was removed *in vacuo*. Water (50 mL) was added and the mixture extracted with ethyl acetate (3 x 50 mL). The extracts were combined and washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give the crude product which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (1.0 g). ^{1}H NMR δ ($CDCl_3$): 2.38 (quin, 2H), 3.79 (s, 3H), 4.20-4.40 (m, 4H), 5.07 (s, 2H), 6.78 (m, 2H), 6.99 (d, 1H), 7.05 (m, 1H), 7.28 (m, 2H), 7.39 (m, 5H), 7.48 (dd, 1H), 7.78 (d, 1H), 8.43 (brs, 1H); *m/z* 517 $(M+H)^+$

3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid



Lithium hydroxide monohydrate (0.27g, 6.5mol) in water (10 mL) was added to a solution of methyl 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-[(phenylmethyl)oxy]benzoate (1.17 g, 2.6 mmol) in THF (20 mL) and the reaction mixture stirred for 2.5 hours at RT. The THF was removed *in vacuo* and the aqueous residue washed with ethyl acetate (20 mL). The aqueous layer was adjusted to pH3 with 1M hydrochloric acid and extracted with ethyl acetate (2 x 50 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to give the desired compound (0.9 g). ^{1}H NMR δ ($CDCl_3$): 2.39 (quin, 2H), 4.20-4.40 (m, 4H), 5.08 (s, 2H), 6.82 (m, 1H), 6.99 (d, 1H), 7.29 (m, 1H), 7.38 (m, 5H), 7.51 (m, 2H), 7.78 (m, 1H), *m/z* 438 $(M+H)^+$

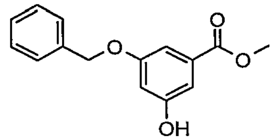
Methyl 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-[(phenylmethyl)oxy]benzoate



A mixture of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (1.54 g, 5.96 mmol), potassium carbonate (1.64 g, 11.91 mmol) and 1-[(3-chloro-4-fluorophenyl)carbonyl]azetidine (0.85 g, 3.97 mmol) in DMF (20 mL) was heated at 120°C for 24 hours. The DMF was removed *in vacuo*, water (50 mL) added and the mixture extracted with ethyl acetate (3 x 50 mL). The extracts were combined and washed with brine (100 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give the crude product which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound. (1.17 g).

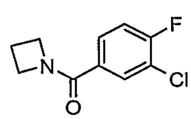
^{1}H NMR δ ($CDCl_3$): 2.38 (quin, 2H), 4.20-4.40 (m, 4H), 5.08 (s, 2H), 6.82 (m, 1H), 6.98 (d, 1H), 7.30 (m, 1H), 7.38 (m, 5H), 7.50 (m, 2H), 7.78 (m, 1H); *m/z* 452 $(M+H)^+$

Methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate



To a stirred solution of methyl 3,5-dihydroxybenzoate (5.95 mol) in DMF (6 L) was added potassium carbonate (9 mol), and the suspension stirred at ambient temperature under argon. To this was added benzyl bromide (8.42 mol) slowly over 1 hour, with a slight exotherm, and the reaction mixture stirred overnight at RT. The reaction was quenched cautiously with ammonium chloride solution (5 L) followed by water (35 L). The aqueous suspension was extracted with DCM (1 x 3 L and 2 x 5 L). The combined extracts were washed with water (10 L) and dried overnight ($MgSO_4$). The solution was evaporated *in vacuo*, and the crude product chromatographed in 3 batches (flash column, 3 x 2 kg silica, eluting with a gradient consisting of hexane containing 10% DCM, to neat DCM, to DCM containing 50% ethyl acetate) to eliminate starting material. The crude eluant was further chromatographed in 175 g batches (Amicon HPLC, 5 kg normal-phase silica, eluting with isohexane containing 20% v/v of ethyl acetate) to give the desired compound (21% yield). ^{1}H NMR δ (d_6-DMSO): 3.8 (s, 3H), 5.1 (s, 2H), 6.65 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.3-7.5 (m, 5H), 9.85 (brs, 1H).

1-[(3-Chloro-4-fluorophenyl)carbonyl]azetidine

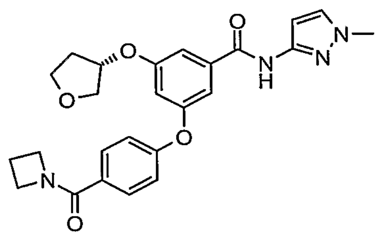


To a solution of 3-chloro-4-fluorobenzoic acid (1.74 g, 10.0 mmol) in DCM (50 mL) was added oxalyl chloride (1.05 mL, 12.0 mmol) and DMF (1 drop). The mixture was stirred at RT for 16 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride and azetidine hydrochloride (1.12 g, 12 mmol) were taken up in DCM (25 mL) and triethylamine (4.18 mL, 30 mmol) added to the mixture, which was stirred at RT for 2 hours. The DCM was evaporated *in vacuo*, and the residue partitioned

between ethyl acetate (100 mL) and 1N hydrochloric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated. The residue was crystallized from ethyl acetate and isohexane to give the title compound (1.64 g).

^{1}H NMR δ ($CDCl_3$): 2.4 (m, 2H), 4.2-4.4 (m, 4H), 7.2 (m, 1H), 7.55 (m, 1H), 7.7 (m, 1H).

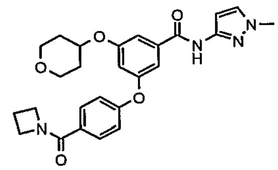
Example 2: 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



A mixture of 3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.26 g, 0.66 mmol), (3*R*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (241 mg, 0.99 mmol) and potassium carbonate (229 mg, 1.66 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave'at 160°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate (50 mL) added. The organics were washed with water (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow foam which was chromatographed on silica, eluting with a gradient of 0-5% methanol in ethyl acetate, to give the desired compound (104 mg).

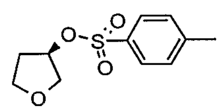
^{1}H NMR δ ($CDCl_3$): 2.18 (m, 1H), 2.25 (m, 1H), 2.48 (quin, 2H), 3.78 (s, 3H), 3.92 (m, 1H), 4.01 (m, 3H), 4.20-4.40 (m, 4H), 4.96 (m, 1H), 6.72 (s, 1H), 6.80 (s, 1H), 7.04 (d, 2H), 7.11 (s, 1H), 7.19 (s, 1H), 7.28 (m, 1H), 7.63 (d, 2H), 8.61 (s, 1H); *m/z* 463 $(M+H)^+$

The following compound was synthesised in an analogous fashion using 3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and tetrahydro-2*H*-pyran-4-yl 4-methylbenzenesulfonate.

Example	Structure	m/z	^{1}H NMR ($CDCl_3$)
2a		477 $(M+H)^+$	δ 1.80 (m, 2H), 2.05 (m, 2H), 2.38 (quin, 2H), 3.60 (m, 2H), 3.82 (s, 3H), 3.99 (m, 2H), 4.20-4.40 (m, 4H), 4.56 (m, 1H), 6.78 (m, 2H), 7.04 (d, 2H), 7.08 (s, 1H), 7.22 (s, 1H), 7.28 (m, 1H), 7.68 (d, 2H), 8.39 (s, 1H)

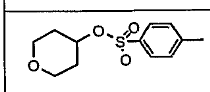
The preparation of (3*R*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate used in **Example 2** is described below:

<u>(3*R*)-Tetrahydrofuran-3-yl 4-methylbenzenesulfonate</u>



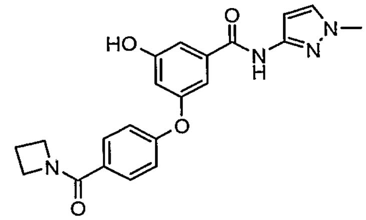
4-Toluene sulfonyl chloride (1.65 g, 8.63 mmol) was added to a solution of *R*-3-hydroxytetrahydrofuran (0.8 g, 9.08 mmol) and pyridine (0.88 mL, 10.9 mmol) in DCM (15 mL). The reaction was stirred at RT for 72 hours. Water (10 mL) and 1M hydrochloric acid (1 mL) were added and the mixture extracted with DCM (15 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered and reduced *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 0-50% ethyl acetate in isohexane, to give the desired compound (1.0 g). ^{1}H NMR δ ($CDCl_3$): 2.13 (m, 2H), 2.47 (s, 3H), 3.80-3.95 (m, 4H), 5.15 (m, 1H), 7.37 (d, 2H), 7.81 (d, 2H).

Tetrahydro-2*H*-pyran-4-yl 4-methylbenzenesulfonate, used in the preparation of **Example 2a**, was synthesised in an analogous fashion:

Structure	m/z	^{1}H NMR ($CDCl_3$)
		δ 1.78 (m, 2H), 1.89 (m, 2H), 2.47 (s, 3H), 3.50 (m, 2H), 3.90 (m, 2H), 4.73 (m, 1H), 7.37 (d, 2H), 7.82 (d, 2H).

The preparation of 3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described below:

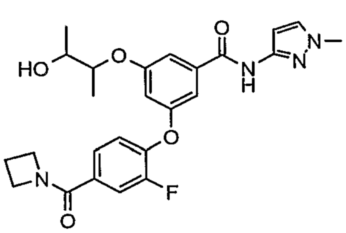
3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A solution of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (1.00 g, 1.93 mmol), 10% by weight palladium on carbon (0.10 g) and triethylamine (0.81 mL, 5.79 mmol), in ethanol (50 mL), was allowed to stir at RT under a hydrogen atmosphere for 16 hours. The solution was filtered through Celite® and washed through with methanol (100 mL). The solution was concentrated *in vacuo*, the residue dissolved in ethanol (50 mL)and 10% by weight palladium on carbon (0.10 g) and triethylamine (0.81 mL, 5.79 mmol) added. The reaction was stirred at RT under a hydrogen atmosphere for 48 hours. The solution was filtered through Celite® and washed through with methanol (100 mL). The filtrate was concentrated *in vacuo* to give the desired compound (0.73 g). ^{1}H NMR δ ($CDCl_3$): 2.27 (quin, 2H), 3.69 (s, 3H), 4.20 (d, 4H), 6.59 (t, 1H), 6.67 (d, 1H), 6.88 (d, 2H), 6.94 (t, 1H), 7.08 (t, 1H), 7.20 (s, 1H), 7.50 (d, 2H), 8.69 (s, 1H); *m/z* 393 $(M+H)^+$

The preparation of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide was described earlier.

Example 3: 3-{[4-(Azetidin-1-ylcarbonyl)-2-fluorophenyl]oxy}-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-{[4-(Azetidin-1-ylcarbonyl)-2-fluorophenyl]oxy}-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1)

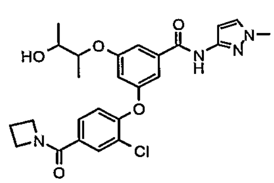


3-Hydroxy-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide - 3-hydroxy-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1) (300 mg, 0.98 mmol), 1-[(3,4-difluorophenyl)carbonyl]azetidine (203 mg, 1.03 mmol) and potassium carbonate (339 mg, 2.45 mmol) in acetonitrile (5 mL) was heated in a microwave reactor at 160°C for 6 hours. The acetonitrile was removed *in vacuo* and the residue dissolved in ethyl acetate (25 mL), washed with water (25 mL), brine (25 mL), dried ($MgSO_4$) and evaporated to a residue that was chromatographed on silica, eluting with 2% methanol in ethyl acetate, to give the required product (87 mg).

^{1}H NMR δ ($CDCl_3$): 1.19 (t, 6H), 1.69 (s, 1H), 2.31 (quin, 2H), 3.69 (s, 3H), 3.78 (quin, 1H), 4.15 (m, 3H), 4.31 (t, 2H), 6.66 (t, 1H), 6.72 (d, 1H), 6.96 (t, 1H), 7.00 (t, 1H), 7.13 (t, 1H), 7.21 (d, 1H), 7.34 (m, 1H), 7.45 (m, 1H), 8.69 (s, 1H); *m/z* 483 $(M+H)^+$

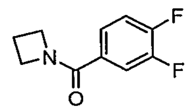
The diastereomers could be separated by chiral preparatory HPLC on a Chiralpak IA (250mm x 20mm) No. EG014 column, eluting with a mixture of isohexane / ethyl acetate / acetic acid / triethylamine (40 / 60 / 0.2 / 0.1), to give the first eluting isomer (63 mg), **Example 3a**, and the second eluting isomer (44 mg), **Example 3b**.

The following compounds was prepared in an analogous fashion from 3-hydroxy-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide - 3-hydroxy-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1) and 1-[(3-chloro-4-fluorophenyl)carbonyl]azetidine.

Example	Structure	*m/z*	^{1}H NMR ($CDCl_3$)
3c		497 $(M+H)^+$	δ 1.17 (t, 6H), 2.29 (quin, 2H), 2.73 (s, 1H), 3.62 (s, 3H), 3.77 (quin, 1H), 4.13 (m, 3H), 4.28 (t, 2H), 6.63 (m, 1H), 6.72 (d, 1H), 6.63 (t, 1H), 6.89 (d, 1H), 6.95 (s, 1H), 7.14 (s, 1H), 7.42 (m, 1H), 7.71 (d, 1H), 9.24 (s, 1H)

The preparation of 1-[(3,4-difluorophenyl)carbonyl]azetidine, used in **Example 3**, is described below:

1-[(3,4-Difluorophenyl)carbonyl]azetidine



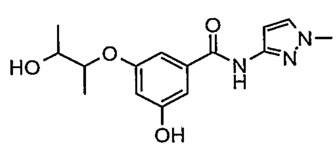
Oxalyl chloride (1.05 mL, 12.0 mmol) was added to a solution of 3,4-difluorobenzoic acid (1.58 g, 10 mmol) in DCM (50 mL) containing DMF (1 drop). The reaction was stirred at RT for 16 hours then evapourated to dryness. The residue was redissolved in DCM (25 mL) and azetidine hydrochloride (1.12 g, 12.0 mmol) added followed by triethylamine (4.18 mL, 30.0 mmol). The mixture was stirred at RT for 2 h then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1N hydrochloric acid, the organic phase washed with a saturated aqueous solution of sodium bicarbonate followed by brine, dried ($MgSO_4$), and concentrated *in vacuo*. The title compound was crystallized from an ethyl acetate and hexane mixture to give a white crystalline solid (1.0 g,).

^1H NMR δ ($CDCl_3$): 2.4 (m, 2H), 4.3 (m, 4H), 7.2 (m, 1H), 7.4 (m, 1H), 7.5 (t, 1H).

The preparation of 1-[(3-chloro-4-fluorophenyl)carbonyl]azetidine, used in **Example 3c**, was described earlier.

The preparation of 3-hydroxy-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1) is described below:

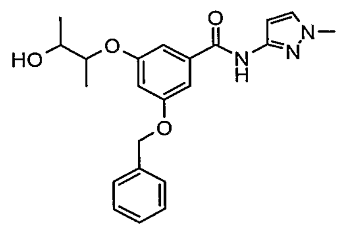
3-Hydroxy-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1)



A solution of a mixture of 3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide and 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (1:1) (1.26 g, 3.19 mmol) and 10% by weight palladium on carbon (0.13 g) in ethanol (50 mL) was allowed to stir at RT under a hydrogen atmosphere for 16 hours. The solution was

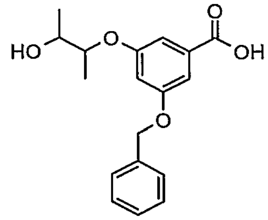
filtered through Celite® and washed through with methanol (100 mL). The solution was concentrated *in vacuo* to give the desired compound (1.03 g). ^{1}H NMR δ (d_6-DMSO): 1.09 (d, 3H), 1.17 (d, 3H), 3.76 (m, 1H), 3.78 (s, 3H), 4.34 (quin, 1H), 6.48 (t, 1H), 6.56 (d, 1H), 6.93 (t, 1H), 7.05 (t, 1H), 7.60 (d, 1H), 9.66 (s, 1H), 10.67 (s, 1H); *m/z* 306 $(M+H)^+$

3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide and 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (1:1)



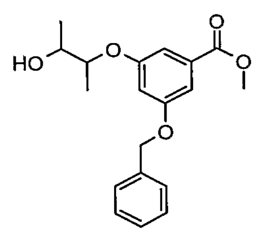
A solution of a mixture of 3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid and 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (1:1) (2.50 g, 7.92 mmol), 1-methyl-1*H*-pyrazol-3-amine (1.54 g, 15.8 mmol), HATU (3.92 g, 10.3 mmol) and DIPEA (2.76 mL, 15.8 mmol) in DMF (15 mL) was stirred at RT and under ambient atmosphere for 16 hours. Water (150 mL) was added and the solution extracted with ethyl acetate (250 mL). The ethyl acetate layer was washed with brine and dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, eluting with 50% ethyl acetate in hexane, to give the desired product (1.26 g). ^{1}H NMR δ ($CDCl_3$): 1.17 (s, 3H), 1.18 (s, 3H), 2.44 (d, 1H), 3.70 (s, 3H), 3.77 (m, 1H), 4.10 (quin, 1H), 4.99 (s, 2H), 6.64 (t, 1H), 6.75 (d, 1H), 6.96 (t, 1H), 7.03 (t, 1H), 7.22 (d, 1H), 7.31 (m, 5H), 8.68 (s, 1H); *m/z* 396 $(M+H)^+$

3-{[(1*R*,2*R*)-2-Hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid and 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (1:1)



To a solution of a mixture of methyl 3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate and methyl 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate (1:1) (2.52 g, 7.63 mmol) in THF (40 mL) was added a solution of lithium hydroxide monohydrate (0.80 g, 19.07 mmol) in water (10 mL). The mixture was allowed to stir at RT for 16 hours. The THF was removed *in vaccuo* and the resulting solution was partitioned between water (100 mL) and ethyl acetate (250 mL). The ethyl acetate layer was washed with brine (50 mL) and dried ($MgSO_4$). The aqueous layer was then adjusted to pH 7 by addition of 1M hydrochloric acid and extracted with ethyl acetate (75 mL). The ethyl acetate layer was washed with brine and dried ($MgSO_4$). The ethyl acetate layers were combined and evaporated to give the required product (2.50 g). ^{1}H NMR δ ($CDCl_3$): 1.18 (s, 3H), 1.20 (s, 3H), 3.80 (quin, 1H), 4.14 (quin, 1H), 5.01 (s, 2H), 6.72 (t, 1H), 7.21 (m, 1H), 7.32 (m, 6H).

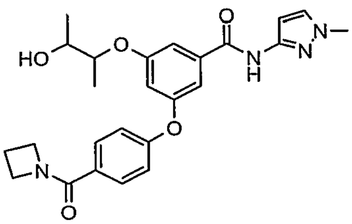
<u>Methyl 3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate and methyl 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate (1:1)</u>



A solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (3.00 g, 11.61 mmol), (2*R*,3*S*)-2,3-dimethyloxirane (3.04 mL, 34.8 mmol), and potassium carbonate (4.02 g, 29.0 mmol) in acetonitrile (60 mL) was heated in a microwave reactor at 150°C for 3 hours. The acetonitrile was removed *in vacuo* and the residual oil dissolved in ethyl acetate (50 mL), washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to a residual oil. The residue was chromatographed on silica, eluting with ethyl acetate, to give the desired compound (2.52 g). ^{1}H NMR δ ($CDCl_3$): 1.17 (d, 6H), 3.82 (s, 3H), 4.04 (q, 2H), 4.99 (s, 2H), 6.67 (t, 1H), 7.14 (s, 1H), 7.30 (m, 6H); *m/z* 330 $(M-H)^-$

The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate was described earlier.

Example 4: 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1)



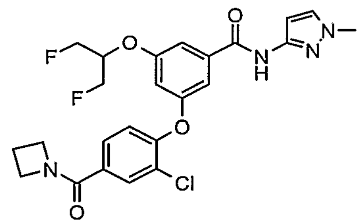
A mixture of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1) (0.140 g, 0.28 mmol) and triethylamine (0.118 mL, 0.84 mmol) in ethanol (10 mL) was evacuated and the atmosphere replaced with argon (3 times). 10% Palladium on carbon (14 mg) was added and the vessel again evacuated and the atmosphere replaced with argon (3 times) and finally evacuated and the atmosphere replaced with hydrogen. The mixture was stirred at RT for 2 days. The reaction mixture was filtered through celite, washed with methanol (50 mL) and the solvents removed *in vacuo*. The residual solid was chromatographed on silica, eluting with 1% methanol in ethyl acetate, to give the desired compound (56 mg).

^{1}H NMR δ ($CDCl_3$): 1.16 (t, 6H), 2.15 (s, 1H), 2.26 (quin, 2H), 3.63 (s, 3H), 3.77 (quin, 1H), 4.13 (m, 3H), 4.26 (t, 2H), 6.65 (t, 1H), 6.71 (d, 1H), 6.90 (d, 2H), 7.02 (t, 1H), 7.15 (t, 1H), 7.19 (d, 1H), 7.55 (d, 2H), 9.18 (s, 1H); *m/z* 465 $(M+H)^+$

The diastereomers could be separated by chiral preparatory HPLC on a Chiralpak IA (250 mm x 20 mm) column, eluting with a mixture of isohexane / ethyl acetate / acetic acid / triethylamine (30 / 70 / 0.2 / 0.1), to give the first eluting isomer (46 mg), **Example 4a**, and the second eluting isomer (44 mg), **Example 4b**.

The preparation of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1) was described earlier.

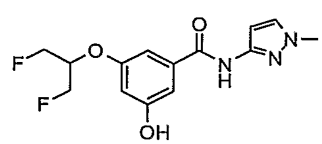
Example 5: 3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A solution of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (350 mg, 1.12 mmol), 1-[(3-chloro-4-fluorophenyl)carbonyl]azetidine (253 mg, 1.18 mmol) and potassium carbonate (388 mg, 2.81 mmol) in acetonitrile (5 mL) was heated in a microwave reactor at 160°C for 6 hours. The acetonitrile was removed *in vacuo* and the residue dissolved in ethyl acetate (25 mL), washed with water (25 mL), brine (25 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate, and then chromatographed by preparative HPLC on C18 reversed phase, eluting with 5-95% acetonitrile (+0.2% TFA) in water (+0.2% TFA), to give the required product (125 mg). ^{1}H NMR δ ($CDCl_3$): 2.31 (quin, 2H), 3.82 (s, 3H), 4.18 (t, 2H), 4.30 (t, 2H), 4.58 (m, 2H), 4.69 (m, 2H), 4.89 (m, 1H), 6.76 (t, 1H), 6.90 (d, 1H), 6.98 (s, 1H), 7.00 (s, 1H), 7.30 (d, 1H), 7.33 (t, 1H), 7.45 (d, 1H), 7.47 (d, 1H), 7.71 (d, 1H), 10.24 (s, 1H); *m/z* 505 $(M+H)^+$

The preparation of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described below:

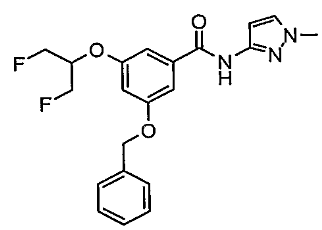
<u>3-{[2-Fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide</u>



A solution of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (2.46 g, 6.13 mmol) and 10% by weigh palladium on carbon (0.246 g) in ethanol (100 mL) was allowed to stir at RT, under a hydrogen

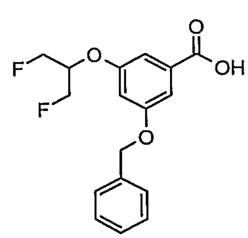
atmosphere overnight. The solution was filtered through Celite® and the cake washed with methanol (100 mL). The solution was evaporated to give the desired compound (1.78 g).
^{1}H NMR δ (d_6-DMSO): 3.78 (s, 3H), 4.72 (m, 4H), 4.97 (m, 1H), 6.57 (d, 2H), 7.03 (s, 1H), 7.16 (s, 1H), 7.59 (s, 1H); *m/z* 312 $(M+H)^+$

3-{[2-Fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



A solution 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (3.00 g, 9.31 mmol), 3-amino-1-methylpyrazole (1.83 g, 18.6 mmol), HATU (4.60 g, 12.1 mmol) and DIPEA (3.25 mL, 18.6 mmol) in DMF (12 mL) was stirred at RT overnight. Water (150 mL) was added and the solution partitioned with ethyl acetate (250 mL). The ethyl acetate layer was separated, washed with brine and dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, eluting with 50% ethyl acetate in isohexane, to give the desired product (2.46 g).
^{1}H NMR δ ($CDCl_3$): 3.69 (s, 3H), 4.57 (m, 5H), 5.00 (s, 2H), 6.70 (t, 1H), 6.74 (d, 1H), 7.01 (t, 1H), 7.08 (t, 1H), 7.21 (d, 1H), 7.30 (m, 5H), 8.68 (s, 1H); *m/z* 402 $(M+H)^+$

3-{[2-Fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid

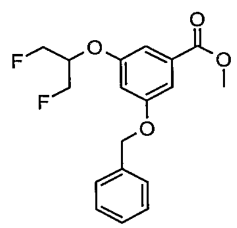


A solution of lithium hydroxide monohydrate (2.32 g, 55.1 mmol) in water (100 mL) was added to a solution of methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoate (7.41 g, 22.0 mmol) in THF (200 mL) and the mixture allowed to stir at RT overnight. The THF was removed *in vacuo* and the resulting solution

partitioned between water (100 mL) and ethyl acetate (250 mL). The ethyl acetate layer was separated, washed with brine and dried ($MgSO_4$). The aqueous layer was then adjusted to pH 7 by addition of 1M hydrochloric acid and extracted with ethyl acetate (75 mL). The ethyl acetate layer was separated, washed with brine and dried ($MgSO_4$). The ethyl acetate layers were combined and evaporated to give the required product (6.40 g).

^1H NMR δ (d_6-DMSO): 4.74 (m, 4H), 5.08 (s, 2H), 6.67 (s, 1H), 6.67 (s, 1H), 7.23 (s, 1H), 7.37 (m, 5H); *m/z* 231 $(M-H)^-$

Methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoate

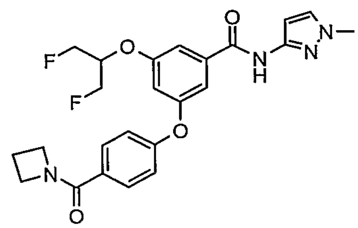


DIAD (7.63 mL, 38.7 mmol) was added in a drop wise fashion to a solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (5.00 g, 19.4 mmol), 1,3-difluoropropan-2-ol (3 mL, 38.7 mmol), and triphenylphosphine (10.16 g, 38.7 mmol) in THF (100 mL) under an inert atmosphere at 0°C. The solution was allowed to reach RT and left to stir for 2 days. The THF was removed *in vacuo* and the residual oil slurried with a mixture of 20% ethyl acetate in isohexane. After allowing to stir for 90 minutes the mixture was filtered and the filtrate evaporated. The residual was oil chromatographed on silica, eluting with 30% ethyl acetate in isohexane, to give the desired compound (7.41 g).

^1H NMR δ (d_6-DMSO): 3.85 (s, 3H), 4.71 (m, 4H), 5.03 (m, 1H), 5.17 (s, 2H), 7.01 (t, 1H), 7.20 (m, 2H), 7.40 (m, 5H); *m/z* 335 $(M-H)^-$

The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate is described earlier.

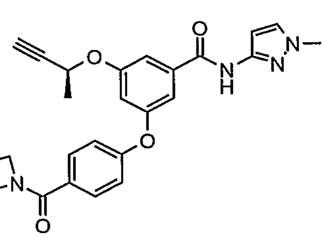
Example 6: 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A solution of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.125 g, 0.25 mmol) and triethylamine (0.104 mL, 0.74 mmol) in ethanol (10 mL) was evacuated and the atmosphere replaced with argon (3 times). 10% Palladium on carbon (12 mg) was added and the vessel again evacuated and the atmosphere replaced with argon (3 times) and finally evacuated and the atmosphere replaced with hydrogen. The mixture was stirred at RT overnight. The reaction mixture was filtered through Celite®, washed with methanol (50 mL) and the solvents were removed *in vacuo*. The residual solid was chromatographed on silica, eluting with ethyl acetate, to give the desired compound (58 mg).
^{1}H NMR δ ($CDCl_3$): 2.29 (quin, 2H), 3.70 (s, 3H), 4.22 (m, 4H), 4.60 (m, 5H), 6.71 (d, 1H), 6.76 (t, 1H), 6.95 (d, 2H), 7.06 (s, 1H), 7.20 (m, 1H), 7.21 (d, 1H), 7.59 (m, 2H), 8.59 (s, 1H); *m/z* 471 $(M+H)^+$

The preparation of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described in **Example 5.**

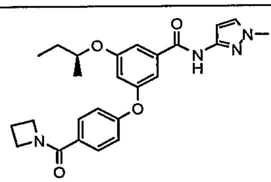
Example 7: 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1*S*)-1-methylprop-2-yn-1-yl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



DIAD (0.141 mL, 0.71 mmol) was added dropwise to a solution of 3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (140 mg, 0.36 mmol), triphenylphosphine (118 mg, 0.71 mmol) and (2*R*)-but-3-yn-2-ol (0.056 mL, 0.71 mmol) in THF (3 mL) under an argon atmosphere at 0°C. The solution was allowed to come to RT and left to stir for 60 hours. The solvent was removed *in vacuo* and the oily residue chromatographed on silica, eluting with ethyl acetate, and then chromatographed by preparative HPLC on C18 reversed phase, eluting with 5-95% acetonitrile (+0.2% TFA) in water (+0.2% TFA), to give the required product (61 mg).

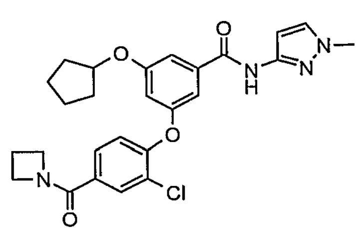
^{1}H NMR δ ($CDCl_3$): 1.60 (d, 3H), 2.31 (quin, 2H), 2.40 (s, 1H), 3.82 (s, 3H), 4.26 (s, 4H), 5.02 (q, 1H), 6.80 (t, 1H), 6.93 (s, 1H), 6.97 (s, 1H), 7.00 (s, 1H), 7.25 (s, 1H), 7.30 (d, 1H), 7.42 (s, 1H), 7.56 (d, 2H), 10.46 (s, 1H); *m/z* 445 $(M+H)^+$

The following compound was prepared in an analogous fashion from 3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and (2*R*)-butan-2-ol.

Example	Structure	*m/z*	^{1}H NMR ($CDCl_3$)
7a		450 $(M+H)^+$	δ 0.90 (t, 3H), 1.24 (d, 3H), 1.63 (m2H), 2.30 (quin, 2H), 3.81 (s, 3H), 3.81 (s, 4H), 4.43 (sextet, 1H), 6.70 (t, 1H), 6.92 (d, 1H), 6.97 (s, 1H), 6.99 (s, 1H), 7.18 (s, 1H), 7.28 (d, 2H), 10.34 (s, 1H)

The preparation of 3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described earlier.

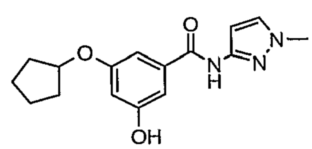
Example 8: 3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-(cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-(Cyclopentyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (200 mg, 0.67 mmol), 1-[(3-chloro-4-fluorophenyl)carbonyl]azetidine (158 mg, 0.80 mmol) and potassium carbonate (184 mg, 1.33 mmol) were dissolved / suspended in acetonitrile (3.5 mL). The reaction mixture was heated for 4 hours at 120°C in a microwave reactor. The mixture was cooled, filtered and concentrated *in vacuo*. The crude product was chromatographed on silica, eluting with 0-5% methanol in DCM, to give the required product as a white foam (133 mg). ^{1}H NMR δ (d_6-DMSO): 1.61 (m, 2H), 1.73 (m, 4H), 1.94 (m, 2H), 2.27 (m,2H), 3.78 (s, 3H), 4.06 (m, 2H), 4.35 (m, 2H), 4.94 (m, 1H), 6.55 (d, 1H), 6.77 (t, 1H), 7.14 (d, 1H), 7.17 (t, 1H), 7.41 (t, 1H), 7.59 (d, 1H), 7.62 (m, 1H), 7.81 (d, 1H), 10.83 (s, 1H); *m/z* 495 $(M+H)^+$

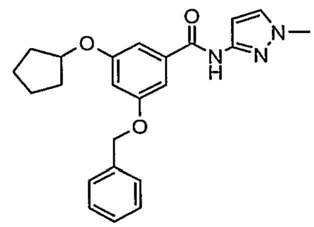
The preparation of 1-[(3-chloro-4-fluorophenyl)carbonyl]azetidine was described earlier. The preparation of 3-(cyclopentyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described below:

3-(Cyclopentyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-(Cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (1.87g, 4.78 mmol) was dissolved in ethanol (40 mL) and 10% palladium on charcoal (102 mg) catalyst added under argon. The reaction was stirred under an atmosphere of hydrogen for 86 hours, then filtered through Celite® and concentrated *in vacuo* to a light brown solid (1.31g). ^{1}H NMR δ (d_6-DMSO): 1.54 (m, 2H), 1.76 (m, 4H), 1.96 (m, 2H), 2.75 (s, 1H), 3.83 (s, 3H), 4.91 (m, 1H), 6.49 (m, 1H), 6.61 (m, 1H), 6.98 (m, 1H), 7.06 (m, 1H), 7.65 (s, 1H), 9.73 (br s, 1H); *m/z* 302 $(M+H)^+$

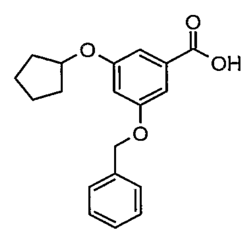
<u>3-(Cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide</u>



3-(Cyclopentyloxy)-5-[(phenylmethyl)oxy]benzoic acid (3.14g, 10.0 mmol), 1-methyl-1H-pyrazol-3-amine (1.95g, 20 mmol) and HATU (4.95g, 13 mmol) were dissolved in DMF (12.5 mL) and DIPEA (3.49 mL, 20 mmol) added. The resultant mixture was stirred at RT for 20 hours. The mixture was quenched with water (150 mL) and extracted with ethyl acetate (2 x 75 mL), washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. The residue was chromatographed on silica, eluting with with 0-30% ethyl acetate in isohexane, to give the desired product as a clear gum (1.87g).

^{1}H NMR δ ($CDCl_3$): 1.59 (m, 4H), 1.83 (m, 4H), 3.79 (s, 3H), 4.76 (m, 1H), 5.08 (s, 2H), 6.66 (t, 1H), 6.82 (m, 1H), 7.01 (m, 1H), 7.08 (m, 1H), 7.26 (m, 1H), 7.33 (m, 1H), 7.35-7.45 (m, 4H), 8.67 (s, 1H); *m/z* 392 $(M+H)^+$

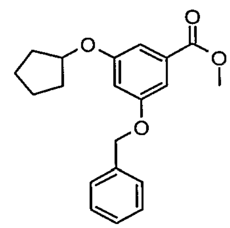
<u>3-(Cyclopentyloxy)-5-[(phenylmethyl)oxy]benzoic acid</u>



Methyl 3-(cyclopentyloxy)-5-[(phenylmethyl)oxy]benzoate (9.25g, 28.34 mmol) was dissolved in THF (120 mL) and a solution of lithium hydroxide mono hydrate (3.49 g, 85.0 mmol) in water (60 mL) added. The bi-phasic solution was stirred at RT for 16 hours (LCMS indicated reaction 80% complete), methanol (15 mL) added and the mixture stirred for a further 4 hours. The THF was removed *in vacuo* then water (40 mL) added and the pH adjusted to 7 with hydrochloric acid. The solid was collected and washed thoroughly with cold water (8.85 g).

^{1}H NMR δ (d_6-DMSO): 1.64 (m, 2H), 1.76 (m, 4H), 1.96 (m, 2H), 4.89 (m, 1H), 5.19 (s, 2H), 6.80 (s, 1H), 7.07 (s, 1H), 7.16 (s, 1H), 7.34-7.53 (m, 5H); *m/z* 311 $(M+H)^+$

Methyl 3-(cyclopentyloxy)-5-[(phenylmethyl)oxy]benzoate

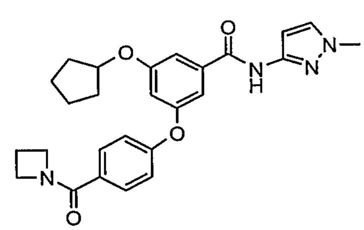


Methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (10 g, 38.7 mmol), 1-cyclopentanol (6.135 mL, 58.07 mmol) and triphenylphosphine (15.24g, 58.07 mmol) were stirred under argon in THF (166 mL) and cooled in an ice bath to 5°C. DEAD (25.3 mL, 58.1 mmol) was added dropwise to the mixture, maintaining the internal temperature in the range 5 – 10°C. Stirring was continued for 16 hours. The mixture was concentrated *in vacuo*, re-dissolved in ethyl acetate (60 mL) and isohexane (60 mL), the resultant precipitate removed and the solution concentrated *in vacuo* to give a yellow oil. The residue was chromatographed on silica, eluting with 0-30% ethyl acetate in isohexane, to give a colourless oil which crystallised to a white solid under vacuum.

^{1}H NMR δ ($CDCl_3$): 1.62 (m, 2H), 1.71-1.98 (m, 6H), 3.90 (s, 3H), 4.76 (m, 1H), 5.08 (s, 2H), 6.69 (m, 1H), 7.16 (m, 1H), 7.23 (m, 1H), 7.29-7.44 (m, 5H); *m/z* 325 $(M+H)^+$

The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate was described earlier.

Example 9: 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-(cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



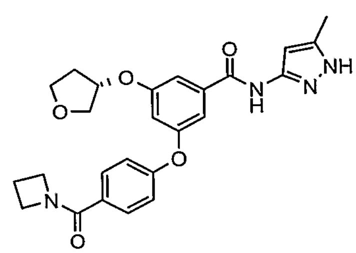
3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-(cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (103 mg, 0.21 mmol) was dissolved in ethanol (10 mL) and 10% palladium on charcoal (9 mg) catalyst added under argon. The mixture was stirred under an atmosphere of hydrogen for 40 hours. The mixture showed incomplete conversion so the

catalyst was removed by filtration, replaced with fresh catalyst and the reaction stirred under an atmosphere of hydrogen for a further 3 days. The mixture was filtered through Celite ® and concentrated *in vacuo*. The residue was chromatographed first on silica, eluting with 0-5% methanol in DCM, then on alumina, eluting with 0-5% methanol in DCM, to give the desired compound as a white foam (22.5 mg).

^{1}H NMR δ (d_6-DMSO): 1.61 (m, 2H), 1.73 (m, 4H), 1.94 (m, 2H), 2.27 (m, 2H), 3.78 (s, 3H), 4.00 (s, 2H), 4.33 (s, 2H), 4.94 (m, 1H), 6.56 (d, 1H), 6.79 (t, 1H), 7.08 (d, 2H), 7.24 (t, 1H), 7.40 (t, 1H), 7.59 (d, 1H), 7.68 (d, 2H), 10.82 (s, 1H); *m/z* 461 $(M+H)^+$

The preparation of 3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-(cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described earlier.

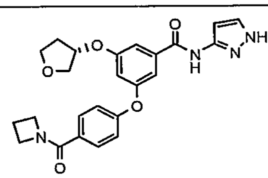
Example 10: 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-*N*-(5-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



1-Chloro-*N,N*,2-trimethyl-1-propenylamine (0.145 mL, 1.10 mmol) was added to a solution of 3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid (350 mg, 0.92 mmol) in DCM (6 mL) and stirred at RT for 30 - 40min. 1,1-Dimethylethyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate (361 mg, 1.83 mmol) and pyridine (0.148 mL, 1.83 mmol) were added and the reaction stirred at RT for 2 hours. The solvent was removed *in vacuo*, water (20 mL) added and the mixture extracted with ethyl acetate (3 x 20 mL). The extracts were combined and washed with 2N hydrochloric acid (20 mL), a saturated solution of sodium bicarbonate (20 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was chromatographed on silica, eluting with a gradient of 0-10% methanol in DCM, to give a white solid which was taken up in acetonitrile (2 mL) and heated in a microwave reactor at 160°C for 10 minutes.

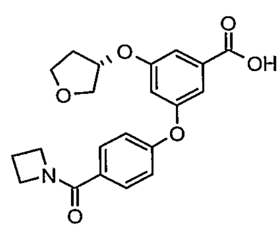
The reaction mixture was evaporated and the residue chromatographed on silica, eluting with 0-5% methanol in DCM, to give the desired compound as a white foam (50 mg). ^{1}H NMR δ ($CDCl_3$): 2.11 - 2.29 (m, 2H), 2.32 (s, 3H), 2.32 - 2.40 (m, 2H), 3.88 - 4.02 (m, 4H), 4.23 (t, 2H), 4.35 (t, 2H), 4.95 - 4.99 (m, 1H), 6.56 (s, 1H), 6.71 (t, 1H), 7.02 (d, 2H), 7.13 (s, 1H), 7.21 (s, 1H), 7.64 (d, 2H), 9.06 (s, 1H); *m/z* 463 $(M+H)^+$, 461 $(M-H)^-$

The following compound was synthesised in an analogus fashion from 3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid and 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate:

Example	Structure	*m/z*	^{1}H NMR ($CDCl_3$)
10a		449 $(M+H)^+$ 447 $(M-H)^-$	δ 2.11 - 2.29 (m, 2H), 2.32 - 2.40 (m, 2H), 3.88 - 4.02 (m, 4H), 4.23 (t, 2H), 4.34 (t, 2H), 4.94 - 4.98 (m, 1H), 5.40 (s, 1H), 6.72 (t, 1H), 6.84 (s, 1H), 7.01 (d, 2H), 7.15 (s, 1H), 7.24 (t, 1H), 7.52 (d, 1H), 7.64 (d, 2H), 9.25 (s, 1H)

The preparation of 3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid is described below.

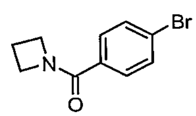
<u>3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid</u>



Cesium carbonate (2.05 g, 6.30 mmol) was added to a solution of methyl 3-hydroxy-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate (500 mg, 2.10 mmol), 1-[(4-bromophenyl)carbonyl]azetidine (605 mg, 2.51 mmol), copper(I) iodide (400 mg, 2.10 mmol) and 2,2,6,6-tetramethyl-3,5-heptanedione (1.8 mL, 8.40 mmol) in NMP (16 mL) and the stirred mixture heated at 160°C in a microwave reactor for 8 hours. The reaction mixture was filtered through diatomaceous earth and the filter pad washed thoroughly with DCM and methanol. The filtrate was concentrated *in vacuo* then azeotroped with toluene.

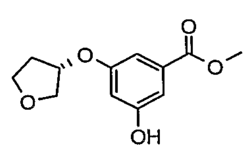
Water was added to the residue and the mixture washed with ethyl acetate (3 x 30 mL). The aqueous phase was acidified with 1N hydrochloric acid then extracted with ethyl acetate (3 x 40 mL). The combined organic phase was washed with water (2 x 10 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the desired compound as a brown residue (1.045 g), which was used without further purification.
^{1}H NMR δ ($CDCl_3$): 2.11 - 2.29 (m, 2H), 2.33 - 2.42 (m, 2H), 3.88 - 4.03 (m, 4H), 4.24 (t, 2H), 4.35 (t, 2H), 4.95 - 4.98 (m, 1H), 6.76 (t, 1H), 7.02 (d, 2H), 7.34 - 7.35 (m, 2H), 7.65 (d, 2H); *m/z* 384 $(M+H)^+$, 382 $(M-H)^-$

1-[(4-Bromophenyl)carbonyl]azetidine



Oxalyl chloride (1.0ml, 12.0 mmol) was added to a solution of 4-bromobenzoic acid (2.01 g, 10.0 mmol) in DCM (25 mL) and the mixture stirred at RT for 18 hours. The DCM was evaporated *in vacuo*, the residue azeotroped with toluene (2 x 5 mL) and added to a solution of azetidine hydrochloride (1.1 g, 12.0 mmol) and triethylamine (5.0 mL, 36.0 mmol) in DCM (50 mL). The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo* and the residue partitioned between water (75 mL) and ethyl acetate (150 mL). The organic layer was washed with 1N hydrochloric acid, a saturated aqueous solution of sodium hydrogen carbonate, brine, dried ($MgSO_4$) and evaporated to a residue which was crystallised from ethyl acetate and iso hexane to give the desired compound as a white solid (1.75 g). ^{1}H NMR δ ($CDCl_3$): 2.3 (m, 2H), 4.2 (m, 4H), 7.45 (dd, 4H).

Methyl 3-hydroxy-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate

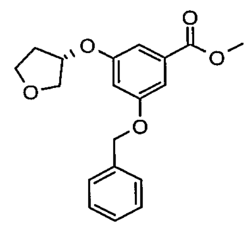


Methyl 3-[(phenylmethyl)oxy]-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate (25.0 g, 76.2 mmol) was dissolved in THF (150 mL) and ethanol (150 mL). 10% Palladium on carbon (30 mg) was added and the mixture placed under a hydrogen atmosphere and left to stir at RT until the reaction was complete. The catalyst was removed by filtration through

diatomaceous earth and the filtrate was concentrated *in vacuo* to give an orange oil which crystallised on standing. The solid was filtered off and washed with diethyl ether to give the desired product as a white solid (13.75 g).

^{1}H NMR δ ($CDCl_3$): 2.1-2.3 (2H, m), 3.9 (3H, s), 3.9-3.95 (2H, m), 3.97-4.05 (2H, m), 4.95 (1H, s), 5.6 (1), 6.6 (1H, t), 7.1 (1H, t), 7.13 (1H, t); *m/z* 237 $(M+H)^+$

Methyl 3-[(phenylmethyl)oxy]-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate

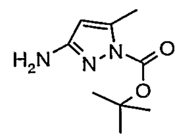


A mixture of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (18.8 g, 72.75 mmol), (3*R*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (18.5 g, 76.4 mmol) and potassium carbonate (20.08 g, 145.5 mmol) in butyronitrile (250 mL) was heated to 130°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate added. The organics were washed with water (40 mL), 0.5M sodium hydroxide solution (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 0-5% methanol in DCM, to give the desired compound as a colourless oil (20.1 g). ^{1}H NMR δ ($CDCl_3$): 2.08 - 2.26 (m, 2H), 3.78 - 4.01 (m, 4H), 3.90 (s, 3H), 4.92 - 4.96 (m, 1H), 5.08 (s, 2H), 6.69 (t, 1H), 7.15 (t, 1H), 7.29 (t, 1H), 7.34 - 7.44 (m, 5H); *m/z* 327 $(M+H)^+$

The preparations of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate and (3*R*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate were described earlier.

The synthesis of 1,1-dimethylethyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate, used in the preparation of **Example 10**, is described below.

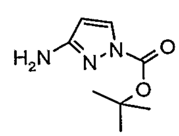
1,1-Dimethylethyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate



5-Methyl-1*H*-pyrazol-3-amine (800 mg, 8.25 mmol) was dissolved in DMF (10 mL) at 0 °C and treated with sodium hydride (336 mg, 8.25 mmol) followed by stirring for a further 30 minutes. Warmed di-*tert*-butyl dicarbonate (1.80 g, 8.25 mmol) was then slowly added via syringe over 5 min and the reaction was allowed to warm to RT and stirred for a further 1 hour. The reaction was taken up in saturated aqueous sodium hydrogencarbonate (50 mL) and ethyl acetate (100 mL). The organic layer was separated then dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography,eluting with 50-100% ethyl acetate in isohexane, afforded the title compound as a colourless oil (380 mg). ^{1}H NMR δ ($CDCl_3$): 1.62 (s, 9H), 2.43 (s, 3H), 3.87 (s, 2H), 5.60 (s, 1H)

The synthesis of 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate, used in the preparation of **Example 10a**, is described below.

1,1-Dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate



1*H*-Pyrazol-3-amine (428 mg, 5.15 mmol) was dissolved in DMF (5 mL) at 0°C and treated with sodium hydride (206 mg, 5.15 mmol) followed by stirring for a further 30 min. Warmed di-tert-butyl dicarbonate (1.12 g, 5.15 mmol) was then slowly added via syringe over 5 min and the reaction was allowed to warm to room temperature and stirred for a further 2 h. The reaction was taken up in saturated aqueous sodium hydrogencarbonate (50 mL) and ethyl acetate (100 mL). The organic layer was separated then dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography (eluting with 1:1 ethyl acetate:hexanes to neat ethyl acetate) afforded the title compound (117 mg) as a white solid. ^{1}H NMR δ ($CDCl_3$): 1.62 (s, 9H), 4.00 (s, 2H), 5.81 (d, 1H), 7.82 (d, 1H)

BIOLOGICAL

Tests:

The biological effects of the compounds of formula (I) may be tested in the following way:

(1) Enzymatic activity

Enzymatic activity of recombinant human pancreatic GLK may be measured by incubating GLK, ATP and glucose. The rate of product formation may be determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the linear increase with time of optical density at 340nm (Matschinsky et al 1993). Activation of GLK by compounds can be assessed using this assay in the presence or absence of GLKRP as described in Brocklehurst et al (Diabetes 2004, **53**, 535-541).

Production of recombinant GLK and GLKRP:

Human GLK and GLKRP cDNA was obtained by PCR from human pancreatic and hepatic mRNA respectively, using established techniques described in Sambrook J, Fritsch EF & Maniatis T, 1989. PCR primers were designed according to the GLK and GLKRP cDNA sequences shown in Tanizawa et al 1991 and Bonthron, D.T. *et al* 1994 (later corrected in Warner, J.P. 1995).

Cloning in Bluescript II vectors

GLK and GLKRP cDNA was cloned in E. coli using pBluescript II, (Short et al 1998) a recombinant cloning vector system similar to that employed by Yanisch-Perron C *et al* (1985), comprising a colEI-based replicon bearing a polylinker DNA fragment containing multiple unique restriction sites, flanked by bacteriophage T3 and T7 promoter sequences; a filamentous phage origin of replication and an ampicillin drug resistance marker gene.

Transformations

E. Coli transformations were generally carried out by electroporation. 400 mL cultures of strains DH5a or BL21(DE3) were grown in L-broth to an OD 600 of 0.5 and harvested by centrifugation at 2,000g. The cells were washed twice in ice-cold deionised water, resuspended in 1mL 10% glycerol and stored in aliquots at -70^{0}C. Ligation mixes

were desalted using Millipore V series™ membranes (0.0025mm) pore size). 40mL of cells were incubated with 1mL of ligation mix or plasmid DNA on ice for 10 minutes in 0.2cm electroporation cuvettes, and then pulsed using a Gene Pulser™ apparatus (BioRad) at 0.5kVcm^{-1}, 250mF. Transformants were selected on L-agar supplemented with tetracyline at 10mg/mL or ampicillin at 100mg/mL.

Expression

GLK was expressed from the vector pTB375NBSE in E.coli BL21 cells,, producing a recombinant protein containing a 6-His tag immediately adjacent to the N-terminal methionine. Alternatively, another suitable vector is pET21(+)DNA, Novagen, Cat number 697703. The 6-His tag was used to allow purification of the recombinant protein on a column packed with nickel-nitrilotriacetic acid agarose purchased from Qiagen (cat no 30250).

GLKRP was expressed from the vector pFLAG CTC (IBI Kodak) in E.coli BL21 cells, producing a recombinant protein containing a C-terminal FLAG tag. The protein was purified initially by DEAE Sepharose ion exchange followed by utilisation of the FLAG tag for final purification on an M2 anti-FLAG immunoaffinity column purchased from Sigma-Aldrich (cat no. A1205).

(2) Oral Glucose Tolerance Test (OGTT)

Oral glucose tolerance tests were done on conscious Zucker obese fa/fa rats (age 12-13 weeks or older) fed a high fat diet (45 % kcal fat) for at least two weeks prior to experimentation. The animals were fasted for 2 hours before use for experiments. A test compound or a vehicle was given orally 120 minutes before oral administration of a glucose solution at a dose of 2 g/kg body weight. Blood glucose levels were measured using a Accucheck glucometer from tail bled samples taken at different time points before and after administration of glucose (time course of 60 minutes). A time curve of the blood glucose levels was generated and the area-under-the-curve (AUC) for 120 minutes was calculated (the time of glucose administration being time zero). Percent reduction in glucose excursion was determined using the AUC in the vehicle-control group as zero percent reduction.

Compounds of the invention generally have an activating activity for glucokinase with an EC_{50} of less than about 500nM. For example, Example 7 has an EC_{50} of 60nM. Example 2 gave a 42% effect in the Oral Glucose Tolerance Test at 10 mg/kg.

REFERENCES

1 Printz, R. L., Magnuson, M. A. and Granner, D. K. (1993) Annual Review of Nutrition **13**, 463-96

2 DeFronzo, R. A. (1988) Diabetes **37**, 667-87

3 Froguel, P., Zouali, H., Vionnet, N., Velho, G., Vaxillaire, M., Sun, F., Lesage, S., Stoffel, M., Takeda, J. and Passa, P. (1993) New England Journal of Medicine **328**, 697-702

4 Bell, G. I., Pilkis, S. J., Weber, I. T. and Polonsky, K. S. (1996) Annual Review of Physiology **58**, 171-86

5 Velho, G., Petersen, K. F., Perseghin, G., Hwang, J. H., Rothman, D. L., Pueyo, M. E., Cline, G. W., Froguel, P. and Shulman, G. I. (1996) Journal of Clinical Investigation **98**, 1755-61

6 Christesen, H. B., Jacobsen, B. B., Odili, S., Buettger, C., Cuesta-Munoz, A., Hansen, T., Brusgaard, K., Massa, O., Magnuson, M. A., Shiota, C., Matschinsky, F. M. and Barbetti, F. (2002) Diabetes **51**, 1240-6

6a Gloyn, A.L., Noordam, K., Willemsen, M.A.A.P., Ellard, S., Lam, W.W.K., Campbell, I. W., Midgley, P., Shiota, C., Buettger, C., Magnuson, M.A., Matschinsky, F.M., and Hattersley, A.T.; Diabetes **52**: 2433-2440

7 Glaser, B., Kesavan, P., Heyman, M., Davis, E., Cuesta, A., Buchs, A., Stanley, C. A., Thornton, P. S., Permutt, M. A., Matschinsky, F. M. and Herold, K. C. (1998) New England Journal of Medicine **338**, 226-30

8 Caro, J. F., Triester, S., Patel, V. K., Tapscott, E. B., Frazier, N. L. and Dohm, G. L. (1995) Hormone & Metabolic Research **27**, 19-22

9 Desai, U. J., Slosberg, E. D., Boettcher, B. R., Caplan, S. L., Fanelli, B., Stephan, Z., Gunther, V. J., Kaleko, M. and Connelly, S. (2001) Diabetes **50**, 2287-95

10 Shiota, M., Postic, C., Fujimoto, Y., Jetton, T. L., Dixon, K., Pan, D., Grimsby, J., Grippo, J. F., Magnuson, M. A. and Cherrington, A. D. (2001) Diabetes **50**, 622-9

11 Ferre, T., Pujol, A., Riu, E., Bosch, F. and Valera, A. (1996) Proceedings of the National Academy of Sciences of the United States of America **93**, 7225-30

12 Seoane, J., Barbera, A., Telemaque-Potts, S., Newgard, C. B. and Guinovart, J. J. (1999) Journal of Biological Chemistry **274**, 31833-8

13 Moore, M. C., Davis, S. N., Mann, S. L. and Cherrington, A. D. (2001) Diabetes Care **24**, 1882-7

14 Alvarez, E., Roncero, I., Chowen, J. A., Vazquez, P. and Blazquez, E. (2002) Journal of Neurochemistry **80**, 45-53

15 Lynch, R. M., Tompkins, L. S., Brooks, H. L., Dunn-Meynell, A. A. and Levin, B. E. (2000) Diabetes **49**, 693-700

16 Roncero, I., Alvarez, E., Vazquez, P. and Blazquez, E. (2000) Journal of Neurochemistry **74**, 1848-57

17 Yang, X. J., Kow, L. M., Funabashi, T. and Mobbs, C. V. (1999) Diabetes **48**, 1763-1772

18 Schuit, F. C., Huypens, P., Heimberg, H. and Pipeleers, D. G. (2001) Diabetes **50**, 1-11

19 Levin, B. E. (2001) International Journal of Obesity **25**, supplement 5, S68-S72.

20 Alvarez, E., Roncero, I., Chowen, J. A., Thorens, B. and Blazquez, E. (1996) Journal of Neurochemistry **66**, 920-7

21 Mobbs, C. V., Kow, L. M. and Yang, X. J. (2001) American Journal of Physiology - Endocrinology & Metabolism **281**, E649-54

22 Levin, B. E., Dunn-Meynell, A. A. and Routh, V. H. (1999) American Journal of Physiology **276**, R1223-31

23 Spanswick, D., Smith, M. A., Groppi, V. E., Logan, S. D. and Ashford, M. L. (1997) Nature **390**, 521-5

24 Spanswick, D., Smith, M. A., Mirshamsi, S., Routh, V. H. and Ashford, M. L. (2000) Nature Neuroscience **3**, 757-8

25 Levin, B. E. and Dunn-Meynell, A. A. (1997) Brain Research **776**, 146-53

26 Levin, B. E., Govek, E. K. and Dunn-Meynell, A. A. (1998) Brain Research **808**, 317-9

27 Levin, B. E., Brown, K. L. and Dunn-Meynell, A. A. (1996) Brain Research **739**, 293-300

28 Rowe, I. C., Boden, P. R. and Ashford, M. L. (1996) Journal of Physiology **497**, 365-77

29 Fujimoto, K., Sakata, T., Arase, K., Kurata, K., Okabe, Y. and Shiraishi, T. (1985) Life Sciences **37**, 2475-82

30 Kurata, K., Fujimoto, K. and Sakata, T. (1989) Metabolism: Clinical & Experimental **38**, 46-51

31 Kurata, K., Fujimoto, K., Sakata, T., Etou, H. and Fukagawa, K. (1986) Physiology & Behavior **37**, 615-20

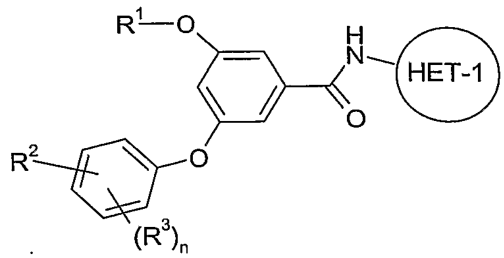
32 Jetton T.L., Liang Y., Pettepher C.C., Zimmerman E.C., Cox F.G., Horvath K., Matschinsky F.M., and Magnuson M.A., J. Biol. Chem., Feb **1994**; **269**: 3641 – 3654.

33 Reimann F. and Gribble F. M., Diabetes **2002** 51: 2757-2763

34 Cheung A. T., Dayanandan B., Lewis J. T., Korbutt G. S., Rajotte R. V., Bryer-Ash M., Boylan M. O., Wolfe M. M., Kieffer T. J., *Science*, Vol 290, Issue 5498, 1959-1962 , 8 December 2000

Claims:

1. A compound of Formula (I):



(I)

wherein:

R^1 is selected from cyclopentyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl and 2-methoxybut-1-yl;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on any nitrogen atom (provided it is not thereby quaternised) by a substituent selected from R^7 and/or on 1 or 2 available carbon atoms by a substituent independently selected from R^6;

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

R^3 is halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 to 7 membered saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from R^8 and/or on an available nitrogen atom by a substituent selected from R^9; or R^4 and R^5 together with the nitrogen atom to which they are attached form a 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an

available carbon by 1 substituent selected from hydroxy, methyl and halo, or on an available nitrogen atom by methyl;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl;

R^7 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl;

R^8 is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl, aminocarbonyl, (1-4C)alkylaminocarbonyl, di(1-4C)alkylaminocarbonyl, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)p(1-4C)alkyl;

R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, aminocarbonyl, (1-4C)alkylaminocarbonyl, di(1-4C)alkylaminocarbonyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)p(1-4C)alkyl;

n is 0 or 1;

p is (independently at each occurrence) 0, 1 or 2;

or a salt thereof.

2. A compound of the formula (I) as claimed in Claim 1 or a salt thereof, wherein

R^1 is selected from but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein HET-1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;

n is 0 or 1;

R^3 is fluoro or chloro;

R^2 is –CONR^{4}R^5;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

3. A compound of the formula (I) as claimed in Claim 1, or a salt thereof, wherein

R^1 is selected from but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl and 2-hydroxybut-1-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein HET-1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;
n is 0 or 1;
R^3 is fluoro or chloro;
R^2 is $-SO_2NR^4R^5$;
R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

4. A compound of the formula (I) as claimed in any one of Claims 1 to 3, or a salt thereof, wherein R^4 and R^5 together form an azetidinyl ring.

5. A compound of formula (I) as claimed in Claim 1, or a salt thereof, wherein:
R^1 is selected from cyclopentyl, 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl and but-2-yl;
HET-1 is pyrazolyl, optionally substituted on carbon or nitrogen by a methyl group;
n is 0 or 1;
R^3 is fluoro or chloro;
R^2 is $-CONR^4R^5$;
R^4 and R^5 together form an azetidinyl ring.

6. A compound of formula (I) as claimed in Claim 5, or a salt thereof, wherein:
R^1 is selected from cyclopentyl, 2-hydroxybut-1-yl, tetrahydrofuryl, tetrahydropyranyl, 2-hydroxy-but-3-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl and but-2-yl;
HET-1 is pyrazolyl or 5-methylpyrazol-3-yl;
n is 0 or 1;
R^3 is fluoro or chloro, particularly chloro;
R^2 is $-CONR^4R^5$;
R^4 and R^5 together form an azetidinyl ring.

7. A compound of the formula (I) as claimed in Claim 1 which is any one or more of the following:
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(2R)-2-hydroxybutyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)-2-fluorophenyl]oxy}-5-{[(1R,2R)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)-2-fluorophenyl]oxy}-5-{[(1S,2S)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1R,2R)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1S,2S)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1R,2R)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1S,2S)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1S)-1-methylprop-2-yn-1-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1S)-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and/or
3-{[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-(cyclopentyloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-5-(cyclopentyloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and/or
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-N-(5-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
3-{[4-(azetidin-1-ylcarbonyl)phenyl]oxy}-N-1H-pyrazol-3-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

or a pharmaceutically-acceptable salt thereof.

8. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 7, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

9. A compound according to any one of Claims 1 to 7 or a pharmaceutically-acceptable salt thereof for use as a medicament.

10. The use of a compound according to any one of Claims 1 to 7, or a pharmaceutically-acceptable salt thereof for the preparation of a medicament for treatment of a disease mediated through GLK.

11. The use of a compound according to any one of Claims 1 to 7, or a pharmaceutically-acceptable salt thereof for the preparation of a medicament for treatment of type 2 diabetes.

12. A method of treating GLK mediated diseases by administering an effective amount of a compound of Formula (I) as claimed in any one of Claims 1 to 7 or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

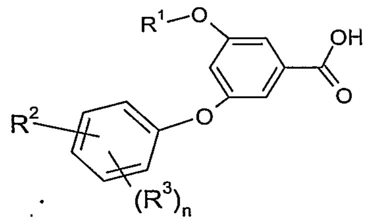
13. The method of Claim 12 wherein the GLK mediated disease is type 2 diabetes.

14. A compound according to any one of Claims 1 to 7 or a pharmaceutically-acceptable salt thereof for use as a medicament for the treatment of a disease mediated through GLK.

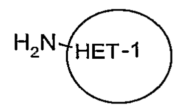
15. A compound according to claim 14 wherein the disease mediated through GLK is type-2 diabetes.

16. A process for the preparation of a compound of Formula (I) as claimed in any one of Claims 1 to 7, which comprises a process a) to d) (wherein the variables are as defined for compounds of Formula (I) in Claim 1 unless otherwise stated):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV), wherein R^1 is as hereinbefore defined or a protected version thereof;



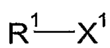
(III)



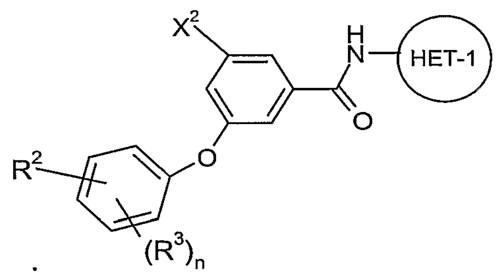
(IV);

or

(b) reaction of a compound of Formula (V) with a compound of Formula (VI),



(V)

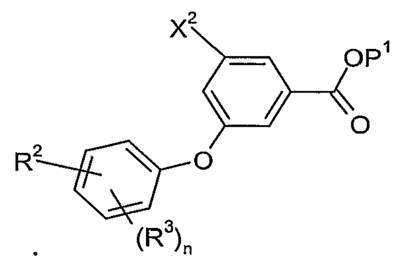


(VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group, and wherein R^1 is as hereinbefore defined or a protected version thereof;

process (b) could also be accomplished using the intermediate ester Formula (VII), wherein P^1 is a protecting group as hereinafter described, followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;

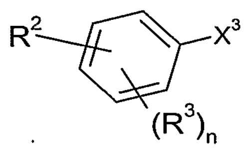
(V)



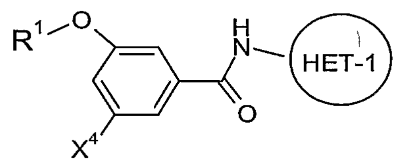
(VII)

or

(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



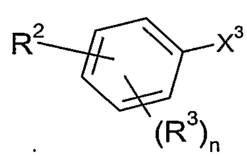
(VIII)



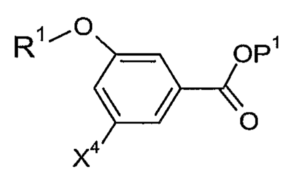
(IX)

wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent, and wherein R^1 is as hereinbefore defined or a protected version thereof;

process (c) could also be accomplished using the intermediate ester Formula (X), followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;

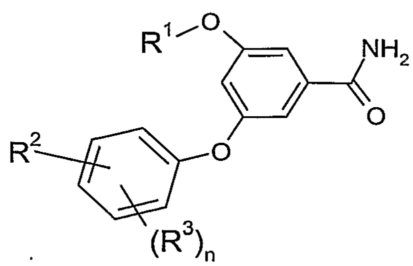


(VIII)

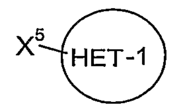


(X)

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



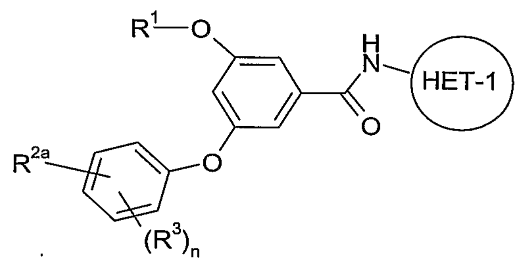
(XI)



(XII);

wherein X^5 is a leaving group; and wherein R^1 is as hereinbefore defined or a protected version thereof; or

e) reaction of a compound of formula (XIII)



(XIII)

wherein R^{2a} is a precursor to R^2, such as a carboxylic acid, ester or anhydride (for R^2 = $-CONR^4R^5$) or the sulfonic acid equivalents (for R^2 is $-SO^2NR^4R^5$); with an amine of formula $-NR^4R^5$;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/002922

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D405/14 A61K31/41 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/076420 A (BANYU PHARMACEUTICAL CO., LTD; IINO, TOMOHARU; HASHIMOTO, NORIAKI; NAK) 10 September 2004 (2004-09-10) Examples, claims -----	1-16
P,A	EP 1 600 442 A (BANYU PHARMACEUTICAL CO., LTD) 30 November 2005 (2005-11-30) the whole document -----	1-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 September 2006	07/09/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fritz, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2006/002922

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/002922

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004076420 A	10-09-2004	AU 2004215514 A1	10-09-2004
		BR PI0407810 A	01-03-2006
		CA 2516407 A1	10-09-2004
		EP 1600442 A1	30-11-2005
		MA 27660 A1	01-12-2005
		MX PA05009059 A	19-10-2005
		US 2006167053 A1	27-07-2006
EP 1600442 A	30-11-2005	AU 2004215514 A1	10-09-2004
		BR PI0407810 A	01-03-2006
		CA 2516407 A1	10-09-2004
		WO 2004076420 A1	10-09-2004
		MA 27660 A1	01-12-2005
		MX PA05009059 A	19-10-2005
		US 2006167053 A1	27-07-2006